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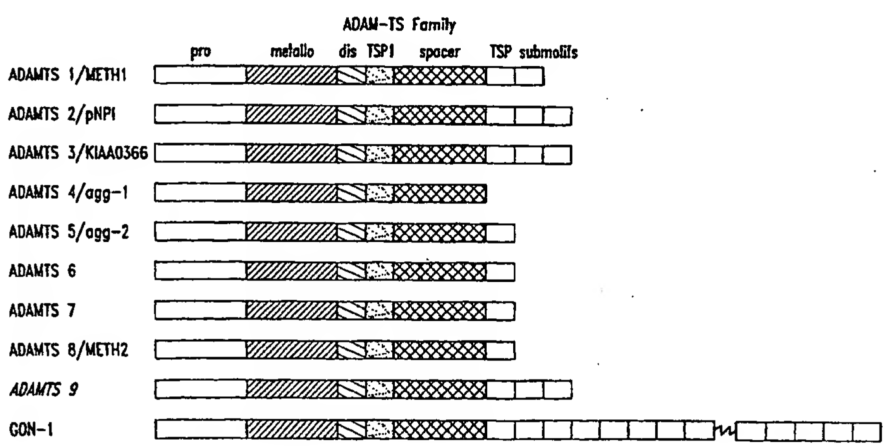

(57) Abstract

Novel members of the ADAMTS family of metalloproteinases are provided, along with variants thereof and agents that modulate an activity of such metalloproteinases. The polypeptides and modulating agents may be used, for example, in the prevention and treatment of a variety of conditions associated with undesirable levels of metalloproteinase activity.

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METALLOPROTEINASES AND METHODS OF USE THEREFOR

TECHNICAL FIELD

The present invention relates generally to compositions and methods for the treatment of conditions associated with undesirable levels of metalloproteinase activity. The invention is more particularly related to metalloproteinases and agents that modulate the activity of such metalloproteinases which may be used, for example, for the therapy of diseases characterized by neuroinflammation and/or neurodegeneration, as well as autoimmune diseases, cancer and inflammation.

BACKGROUND OF THE INVENTION

The ADAMs (A Disintegrin and Metalloproteinase Domain) are a family of proteins that have both a metalloproteinase domain and disintegrin domain. The ADAMs are membrane anchored proteins that contain homology to snake venom metalloproteases (SVMPs) and disintegrins. This family of proteins now contains over 20 members that have a wide variety of important proteolytic and cell fusion functions. ADAM 17/TACE and ADAM 10/Kuz function as proteases that cleave membrane bound tumor necrosis factor (TNF) and the extracellular domain of Notch, respectively. Other ADAM family members, such as ADAM 1/fertilin α, are proteolytically processed to remove the metalloprotease domain but retain the disintegrin domain. This protein has been shown to be essential for sperm-egg cell fusion.

A closely related family called ADAMTS contains a thrombospondin domain in addition to the disintegrin and metalloproteinase domains. ADAMTS-1, for example, is expressed in association with inflammatory processes and in a cachexigenic colon carcinoma cell line (*see* Kuno et al., *J. Biol. Chem. 272*:556-562, 1997; Kuno et al., *Genomics 46*:466-471, 1997). This protein appears to be secreted from the cell and subsequently associated with the extracellular matrix (ECM).

While the function of ADAMTS-1 and many of the ADAM proteins is not known, it has been shown that ADAM 17 (TACE) processes TNF from the surface of the cell (*see* Black et al., *Nature 385*:729-733, 1997). ADAM 10 (Kuzbanian) has

also been shown to cleave TNF from the cell surface (Rosendahl et al., *J. Biol. Chem. 272*:24588-24593, 1997). ADAM 10 may be involved in the cleavage of other cell surface proteins as well. In Drosophila, ADAM 10 has been reported to cleave the cell surface proteins Notch (Pan and Rubin, *Cell 90*:271-280, 1997) and Delta (Qi et al., *Science 283*:91-94, 1999). Based largely on these results it is thought that ADAMs proteases are involved in the cleavage of proteins, including growth factors, cytokines and proteoglycans, from the cell surface.

Metalloproteinase activity has been linked to cancer metastasis. The activity of metalloproteinases can contribute to the development of neurodegeneration and inflammation as well. In order to develop agents capable of selectively modulating the activity of a metalloproteinase that contributes to a human disease, it is important to identify and characterize additional metalloproteinases, such as members of the ADAMTS family, and agents that modulate an activity of such metalloproteinases. The present invention fulfills this need and further provides other related advantages.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides ADAMTS polypeptides, and methods employing such polypeptides. Within certain aspects, isolated polynucleotides that encode an ADAMTS polypeptide are provided. Certain ADAMTS polynucleotides encode an ADAMTS polypeptide that comprises: (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein. Such polynucleotides may, within certain embodiments, comprise a sequence recited in any one of SEQ ID NOs:1, 3, 9, 13, 15, 17, 21, 23 or 25.

Within related aspects, the present invention provides recombinant expression vectors comprising an ADAMTS polynucleotide, as well as host cells transformed or transfected with such an expression vector.

The present invention further provides isolated antisense polynucleotides complementary to at least 20 consecutive nucleotides present within an ADAMTS polynucleotide.

Within further aspects, methods are provided for preparing an ADAMTS polypeptide, comprising the steps of: (a) culturing a host cell transformed or transfected with an expression vector comprising a polynucleotide that encodes an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; wherein the step of culturing is performed under conditions promoting expression of the polynucleotide sequence; and (b) recovering an ADAMTS polypeptide.

The present invention further provides isolated ADAMTS polypeptides comprising: (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein. Such an ADAMTS polypeptide may have an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein. ADAMTS polypeptide may comprise an amino acid sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are

present at no more than 10% of the consecutive residues of the ADAMTS protein; and (b) a physiologically acceptable carrier.

Vaccines are also provided, comprising: (a) an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and (b) a non-specific immune response enhancer.

Within further aspects, the present invention provides isolated antibodies, or antigen-binding fragments thereof, that specifically bind to an ADAMTS polypeptide comprising a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

The present invention further provides methods for screening for agents that modulate ADAMTS protein expression or activity. Within certain such aspects, methods are provided for screening for an agent that modulates ADAMTS protein expression in a cell, comprising: (a) contacting a candidate modulator with a cell expressing an ADAMTS polypeptide, wherein the polypeptide comprises: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and (b) subsequently evaluating the effect of the candidate modulator on expression of an ADAMTS mRNA or polypeptide, and therefrom identifying an agent that modulates ADAMTS protein expression in the cell. Similar screens may be performed using a cell comprising an ADAMTS gene promoter operably linked to a reporter gene, and evaluating the effect of a candidate modulator on expression of the reporter gene.

Within further such aspects, methods are provided for screening for an agent that modulates an ADAMTS protein activity, comprising: (a) contacting a

candidate modulator with an ADAMTS polypeptide, comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein; and wherein the step of contacting is carried out under conditions and for a time sufficient to allow the candidate modulator to interact with the polypeptide; and (b) subsequently evaluating the effect of the candidate modulator on an ADAMTS activity of the polypeptide, and therefrom identifying an agent that modulates an activity of an ADAMTS protein.

ADAMTS polynucleotides, polypeptides and modulating agents may be used for a variety of therapeutic applications. Within certain aspects, methods are provided herein for inhibiting neuroinflammation and/or neurodegeneration in a patient, comprising administering to a patient an agent that decreases an activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27. Certain such agents may inhibit expression of an endogenous ADAMTS gene or may bind to an ADAMTS protein.

Within related aspects, methods are provided for treating a patient afflicted with a condition associated with neuroinflammation and/or neurodegeneration, comprising administering to a patient a pharmaceutical composition as described above, and thereby alleviating one or more symptoms of a condition associated with neuroinflammation and/or neurodegeneration. Such conditions include Alzheimer's disease, Parkinson's disease and stroke.

Methods are further provided for treating a patient afflicted with a condition associated with cell proliferation, cell migration, inflammation and/or angiogenesis, comprising administering to a patient a pharmaceutical composition as described above and thereby alleviating one or more symptoms of a condition associated with neuroinflammation and/or neurodegeneration.

Within further aspects, methods are provided for treating a patient afflicted with an invasive tumor, a brain tumor or a brain injury, comprising administering to a patient an agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Methods are further provided for modulating ADAMTS expression and/or activity in a cell, comprising contacting a cell expressing an ADAMTS polypeptide with an effective amount of an agent that modulates ADAMTS activity, wherein the ADAMTS polypeptide comprises: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and thereby modulating ADAMTS expression and/or activity in the cell.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-2 (SEQ ID NO:1).

Figure 2 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-2 (SEQ ID NO:2).

Figures 3A-3B present a partial sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-4 (SEQ ID NO:3).

Figure 4 presents a partial predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-4 (SEQ ID NO:4).

Figures 5A and 5B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0605 (SEQ ID NO:5).

Figure 6 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0605 (SEQ ID NO:6).

Figures 7A and 7B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0366 (SEQ ID NO:7).

Figure 8 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0366 (SEQ ID NO:8).

Figures 9A and 9B present the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-3 (SEQ ID NO:9).

Figure 10 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-3 (SEQ ID NO:10).

Figures 11A and 11B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0688 (SEQ ID NO:11).

Figure 12 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0688 (SEQ ID NO:12).

Figure 13 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-5 (SEQ ID NO:13).

Figure 14 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-5 (SEQ ID NO:14).

Figure 15 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-4 (SEQ ID NO:15).

Figure 16 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-4 (SEQ ID NO:16).

Figures 17A-17G present a sequence alignment of human ADAMTS-1 (SEQ ID NO:28), ADAMTS-2 (SEQ ID NO:2), ADAMTS-3 (SEQ ID NO:10), ADAMTS-4 (SEQ ID NO:4), KIAA0688 (SEQ ID NO:12), KIAA0366 (SEQ ID NO:8) and KIAA0605 (SEQ ID NO:6).

Figure 18 presents the sequence of a polynucleotide encoding the representative bovine metalloproteinase ADAMTS-4 (SEQ ID NO:17).

Figure 19 presents the predicted amino acid sequence of the representative bovine metalloproteinase ADAMTS-4 (SEQ ID NO:18).

Figure 20 presents the sequence of a polynucleotide encoding the representative bovine metalloproteinase KIAA0688 (SEQ ID NO:19).

Figure 21 presents the predicted amino acid sequence of the representative bovine metalloproteinase KIAA0688 (SEQ ID NO:20).

Figure 22 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-5 (SEQ ID NO:21).

Figure 23 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-5 (SEQ ID NO:22).

Figure 24 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-2 (SEQ ID NO:23).

Figure 25 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-2 (SEQ ID NO:24).

Figure 26 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-3 (SEQ ID NO:25).

Figure 27 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-3 (SEQ ID NO:26).

Figure 28 is a photograph depicting a coumassie blue-stained gel following electrophoresis of 500 micrograms brevican, previously incubated with and without ADAMTS-4 (TS-4) as indicated.

Figure 29 depicts the amino acid sequence of ADAMTS-9 (SEQ ID NO:27). The predicted signal sequence is underlined. The Zn binding, met turn, TSP 1 motif and TSP-1 like submotifs are shaded. Two potential furin cleavage sites are in parenthesis with the most likely cleavage site shaded. A potential "cysteine switch" amino acid is indicated with a star. The start of each domain is indicated with an arrow.

Figures 30A-30C illustrate the comparison of ADAMTS-9 to other ADAMTS family members. In Figure 30A, the domain structure of human ADAMTS 9 is compared to human ADAMTS 1-8, and also with the *C. elegans* GON-1 protein. The pro-domain, metalloprotease domain, disintegrin-like domain, initial TSP type 1

repeat, spacer region, and TSP1 like submotifs are outlined. Figure 30B shows the consensus sequence for Zn binding in the metalloprotease domain (SEQ ID NO:30), along with the Zn binding site for various ADAM and ADAM-TS proteins (SEQ ID Nos: 42-48, 50) that have active metalloprotease domains for comparison to ADAMTS-9 (SEQ ID NO:49). Conserved residues are shaded. Figure 30C is a dendrogram showing the phyllogenetic relationship between the protein sequence of the known ADAM-TS human family members and GON-1 from *C. elegans*.

Figure 31 is a photograph illustrating the tissue distribution pattern of ADAMTS-9 in human fetal and adult cDNA. PCR analysis of several human fetal and adult cDNAs was performed using specific primers to ADAMTS 9. Lanes 2 -16 are human adult tissue cDNAs and lanes 17 - 24 are human fetal cDNAs. Lane 25 is a no cDNA control. The expected product size for these ADAMTS 9 primers is 510 bp. The lower panel contains the same cDNA samples used as a template for PCR with G3PDH primers (expected product size is 1 kb).

Figures 32A and 32B illustrate the chrommosomal localization of human ADAMTS-9 to 3p14.3-21.1. Figure 32A is a photograph showing the results of FISH analysis in which a genomic ADAMTS 9 probe hybridized to chromosome 3p. Figure 32B shows two identogams illustrating the chromosomal position of ADAMTS-9 at 3p14.2-14.3. The International System for Human Cytogenetic Nomenclature 1995 was used.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to polypeptides comprising a member of the ADAMTS family of metalloproteinases, or a variant thereof. Such ADAMTS polypeptides are generally characterized by homology to a known ADAMTS protein, and by the presence of one or more of: (a) a disintegrin domain, (b) a zinc-dependent metalloproteinase domain, (c) an ECM domain and/or (d) a thrombospondin type I motif, which may be identified as described herein. The present invention further provides ADAMTS polynucleotides encoding such polypeptides and agents that modulate an activity of such polypeptides. ADAMTS

polypeptides, polynucleotides and/or modulating agents may generally be used for treating conditions associated with undesirable levels of metalloproteinase activity.

ADAMTS POLYNUCLEOTIDES

Any polynucleotide that encodes an ADAMTS polypeptide as described herein is encompassed by the present invention. Such polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

ADAMTS polynucleotides may comprise a native ADAMTS sequence (*i.e.*, an ADAMTS gene that can be found in an organism that is not genetically modified), or may comprise a variant of such a sequence. Native ADAMTS sequences encompassed by the present invention include DNA and RNA molecules that comprise a sequence recited in any one of SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 or 25 as well as homologues thereof from other species and other native ADAMTS sequences that may be identified based on homology to a sequence recited herein. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that an ADAMTS activity of the encoded polypeptide is not diminished, relative to a native ADAMTS protein. The effect on an activity of the encoded polypeptide may generally be assessed as described herein. Preferred variants contain nucleotide substitutions, deletions, insertions and/or additions at no more than 30%, preferably at no more than 20% and more preferably at no more than 10%, of the nucleotide positions. Certain variants are substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding an ADAMTS polypeptide (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed

by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS). Such hybridizing DNA sequences are also within the scope of this invention.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention.

A portion of a sequence complementary to a coding sequence (*i.e.*, an antisense polynucleotide) may also be used as a probe or to modulate gene expression. Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes. Antisense oligonucleotides may be synthesized directly, or cDNA constructs that can be transcribed into antisense RNA may be introduced into cells or tissues to facilitate the production of antisense RNA. Antisense oligonucleotides are preferably at least 20 nucleotides in length, preferably at least 30 nucleotides in length. A portion of a coding sequence or a complementary sequence may also be designed as a probe or primer to detect gene expression. Probes may be labeled by a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers are preferably 22-30 nucleotides in length.

ADAMTS polynucleotides may be prepared using any of a variety of techniques. For example, an ADAMTS polynucleotide may be amplified from cDNA prepared from cells that express an ADAMTS protein (*e.g.*, microglia, macrophages, myeloid cells, lymphocytes, astrocytes oligodendrocytes, glial cells, neurons, epithelial cells and/or endothelial cells). Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed

based on the sequences provided herein, and may be purchased or synthesized. An amplified portion may then be used to isolate a full length gene from a human genomic DNA library or from a suitable cDNA library, using well known techniques. Alternatively, a full length gene can be constructed from multiple PCR fragments. ADAMTS polynucleotides may also be prepared by synthesizing oligonucleotide components (which may be derived from sequences provided herein), and ligating components together to generate the complete polynucleotide. One other approach is to screen a library with a synthesized oligonucleotide that hybridizes to an ADAMTS gene. Libraries may generally be prepared and screened using methods well known to those of ordinary skill in the art, such as those described in Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. It has been found, within the context of the present invention, that ADAMTS genes are expressed in glia. Accordingly, one suitable library is a microglia (*e.g.*, rat) cDNA library. Other libraries that may be employed will be apparent to those of ordinary skill in the art.

As noted above, polynucleotides comprising portions and other variants of native ADAMTS sequences are within the scope of the present invention. Such polynucleotides may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding an ADAMTS polypeptide, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Variants may also be generated by mutagenesis or enzymatic digestion of native sequences. Certain polynucleotides may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a polynucleotide may be administered to a patient such that the encoded polypeptide is generated *in vivo*.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional

bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (*e.g.,* avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for polynucleotides for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.,* an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

ADAMTS POLYPEPTIDES

As used herein, the term "ADAMTS polypeptide" encompasses amino acid chains of any length. For example, an ADAMTS polypeptide may comprise a full length endogenous (*i.e.*, native) ADAMTS protein. Such an ADAMTS polypeptide may consist entirely of a native ADAMTS sequence, or may contain additional heterologous sequences. Native ADAMTS proteins may generally be identified based on sequence homology to known ADAMTS protein sequences, such as the representative sequences provided herein, particularly within disintegrin, metalloproteinase and/or thrombospondin motifs. In general, a protein is considered to be an ADAMTS protein if at least 20 consecutive amino acid residues, preferably 40 consecutive amino acids, are identical to a known ADAMTS protein. Alternatively, or in addition, an ADAMTS protein may comprise at least 100 consecutive amino acids that are substantially similar to residues within a known ADAMTS metalloproteinase. "Substantial similarity," as used herein, refers to a sequence that is at least 50% identical, and preferably at least 80% identical.

An ADAMTS protein further comprises one or more of: (a) a disintegrin domain, (b) a zinc-dependent metalloproteinase domain and/or (c) a thrombospondin type I motif; and displays at least one, activity characteristic of such a domain or motif. In general a disintegrin domain serves as an integrin binding loop and has a sequence similar to AVN(E/D)CD (SEQ ID NO:29). Disintegrin domains can also contain the sequence RGD. The metalloproteinase domain is based on the presence of an extended catalytic site consensus sequence (HEXXHXXGXXHD; SEQ ID NO:30). It is thought that the three histidines bind the zinc, the glutamic acid is the catalytic base and the glycine allows an important structural turn (Stocker et al., *Protein Science 4*:823-840, 1995). The thrombospondin domain contains the sequence motif CSRTCG (SEQ ID NO:31).

Another domain that may be present within an ADAMTS protein is a domain that binds to the extracellular matrix. This has been referred to as the ECM domain and has the semiconserved sequence FREEQC (SEQ ID NO:32).

In certain embodiments, amino acid residues within a "substantially similar" region may contain primarily or entirely conservative substitutions. A conservative substitution is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity on polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

An ADAMTS polypeptide may comprise a portion of a native ADAMTS protein. Such a portion is preferably at least 20 consecutive amino acid residues in length, more preferably at least 50 consecutive amino acid residues in length. Within certain embodiments, the portion retains an ADAMTS activity that is not substantially diminished relative to the full length ADAMTS protein. Certain ADAMTS polypeptides comprise a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Alternatively, an ADAMTS polypeptide may comprise a variant of an ADAMTS protein or portion thereof. A "variant" is a polypeptide that differs in sequence from a native ADAMTS protein only in substitutions, deletions, insertions and/or additions. Within certain embodiments, substitutions are made (if at all) at no more than 30%, preferably at no more than 20% and more preferably at no more than 10% of residues within a portion of a native ADAMTS protein, as described above. Substitutions are preferably conservative, as described above. Substitutions, deletions and/or amino acid additions may be made at any location(s) in the polypeptide,

provided that the modification does not diminish at least one ADAMTS activity. Thus, a variant may comprise only a portion of a native ADAMTS sequence. In addition, or alternatively, variants may contain additional amino acid sequences (such as, for example, linkers, tags and/or ligands), preferably at the amino and/or carboxy termini. Such sequences may be used, for example, to facilitate purification, detection or cellular uptake of the polypeptide.

Certain variants retain an activity of the native ADAMTS protein. In other words, the variant has a metalloproteinase activity; (2) functions as an integrin ligand (*i.e.*, binds to an integrin), as determined by any standard binding assay; and/or (3) retains a functional thrombospondin motif. Such a variant may have an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein. In other words, the ADAMTS activity of the variant may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein.

Also encompassed by the present invention are splice variants of an ADAMTS protein. Such variants may have one or more of the domains described herein deleted, or one or more such domains may be replaced by a domain providing a different function. Such splice variants may be identified using amplification or hybridization techniques described herein.

Dominant negative forms of ADAMTS proteins are also provided. Such forms include fragments and variants of an ADAMTS protein that, when introduced to a cell expressing a native ADAMTS protein, inhibit an activity of the native protein. Inhibition of ADAMTS protein activity may be assessed as described herein.

In general, ADAMTS polypeptides may be prepared using any of a variety of techniques that are well known in the art. For example, polypeptides of the present invention may be prepared by expression of recombinant DNA encoding the polypeptide in cultured host cells. Preferably, the host cells are bacteria, yeast, insect or mammalian cells. The recombinant DNA may be cloned into any expression vector suitable for use within the host cell and transfected into the host cell using techniques well known to those of ordinary skill in the art. An expression vector generally contains

a promoter sequence that is active in the host cell. A tissue specific promoter may also be used, as long as it is activated in the target cell. Preferred promoters express the polypeptide at high levels.

Optionally, the construct may contain an enhancer, a transcription terminator, a poly(A) signal sequence, a bacterial or mammalian origin of replication and/or a selectable marker, all of which are well known in the art. Enhancer sequences may be included as part of the promoter region used or separately. Transcription terminators are sequences that stop RNA polymerase-mediated transcription. The poly(A) signal may be contained within the termination sequence or incorporated separately. A selectable marker includes any gene that confers a phenotype on the host cell that allows transformed cells to be identified. Such markers may confer a growth advantage under specified conditions. Suitable selectable markers for bacteria are well known and include resistance genes for ampicillin, kanamycin and tetracycline. Suitable selectable markers for mammalian cells include hygromycin, neomycin, genes that complement a deficiency in the host (*e.g.* thymidine kinase and TK^- cells) and others well known in the art.

ADAMTS polypeptides may be expressed in transfected cells by culturing the cell under conditions promoting expression of the transfected polynucleotide. Appropriate conditions will depend on the specific host cell and expression vector employed, and will be readily apparent to those of ordinary skill in the art. For commercially available expression vectors, the polypeptide may generally be expressed according to the manufacturer's instructions. Expressed polypeptides of this invention are generally isolated in substantially pure form. Preferably, the polypeptides are isolated to a purity of at least 80% by weight, more preferably to a purity of at least 95% by weight, and most preferably to a purity of at least 99% by weight. In general, such purification may be achieved using, for example, the standard techniques of ammonium sulfate fractionation. SDS-PAGE electrophoresis, and/or affinity chromatography.

Such techniques may be used to prepare native polypeptides or variants thereof. For example, variants of a native polypeptide may generally be prepared from

polynucleotide sequences modified via standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis, and sections of the DNA sequence may be removed to permit preparation of truncated polypeptides. Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptides and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

EVALUATION OF ADAMTS ACTIVITY

As noted above, native ADAMTS proteins and certain variants thereof possess ADAMTS activity. In other words, such polypeptides (1) possess metalloproteinase activity; (2) are capable of interacting with integrin and/or (3) retain a functional thrombospondin motif. Metalloproteinase activity may generally be evaluated by combining an ADAMTS polypeptide with a suitable substrate, and detecting proteinase activity using any standard technique (*e.g.*, Western blot analysis). In general, a variant of an ADAMTS protein that contains a metalloproteinase domain is said to retain metalloproteinase activity if it displays metalloproteinase activity that is not substantially diminished relative to the metalloproteinase activity of the native

ADAMTS protein. In other words, such activity may be enhanced, unchanged or diminished by less than 10%, relative to the activity of the native ADAMTS protein.

The ability of an ADAMTS protein variant to interact with integrin may be assessed using standard binding assays to detect interaction with a purified recombinant integrin or a cell expressing one or more integrins, either naturally or as a result of transfection with genes encoding an integrin (*see* Almeida et al., *Cell 81*:1095-1104, 1995; Chen et al., *J. Cell Biol. 144*:549-561, 1999). Antibodies against various integrins can also be used to interfere with disintegrin-integrin binding and used to further demonstrate specificity of the interaction. In general, a variant of an ADAMTS protein is said to retain the ability to interact with an integrin if such interaction is not substantially diminished relative to the interaction between a native ADAMTS protein and the integrin. In other words, the level of such an interaction may be enhanced, unchanged or diminished by less than 10%, relative to the activity of the native ADAMTS protein.

Thrombospondins have been shown to function in cell adhesion, cell migration, cell proliferation and angiogenesis. A functional thrombospondin motif may be confirmed based on any assay designed to assess such a function. For examples, an ADAMTS protein may inhibit endothelial cell migration, or may inhibit angiogenesis (*e.g.*, in a rat cornea model; *see* Nishimori et al., *Oncogene 15*:2145-2150, 1997). Alternatively, a functional thrombospondin motif may be detected using an assay to measure binding to CD36 (*see* Dawson et al., *J. Cell. Biol. 138*:707-717, 1997). Within any such assay, a variant of an ADAMTS protein is said to have a functional thrombospondin motif if the detected thrombospondin function is not substantially diminished relative to that of the native ADAMTS protein. In other words, the function may be enhanced, unchanged or diminished by less than 10%, relative to that of the native ADAMTS protein.

ADAMTS POLYPEPTIDE MODULATING AGENTS

The present invention further provides agents capable of modulating ADAMTS activity. Such agents may function by modulating ADAMTS transcription

or translation, by stabilizing or destabilizing an ADAMTS protein, or by directly inhibiting or enhancing an activity of an ADAMTS protein. Alternatively, an agent may interact with a substrate for the metalloproteinase or with an integrin involved in and interaction with the disintegrin domain of an ADAMTS protein. Preferably, a modulating agent has a minimum of side effects and is non-toxic. For some applications, agents that can penetrate cells or that are targeted to interstitial spaces are preferred.

Modulating agents include substances that selectively bind to an ADAMTS protein. Such substances include antibodies and antigen-binding fragments thereof (*e.g.*, $F(ab)_2$, Fab, Fv, V_H or V_K fragments), as well as single chain antibodies, multimeric monospecific antibodies or fragments thereof and bi- or multi-specific antibodies and fragments thereof. Antibodies that bind to an ADAMTS protein may be polyclonal or monoclonal, and are specific for an ADAMTS polypeptide (*i.e.*, bind to such a peptide detectable within any appropriate binding assay, and do not bind to an unrelated protein in a similar assay under the same conditions). Preferred antibodies are those antibodies that function as modulating agents to inhibit or block an ADAMTS activity *in vivo*. Antibodies may also be employed within assays for detecting the level of ADAMTS protein within a sample.

Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art (*see, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988). In one such technique, an immunogen comprising the polypeptide is initially injected into a suitable animal (*e.g.*, mice, rats, rabbits, sheep and goats), preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* *6*:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of

producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction.

Once a cell line, such as a hybridoma, expressing an antibody that specifically binds to an ADAMTS protein has been obtained, other chimeric antibodies and fragments thereof as described herein may be prepared. Using well known techniques, a cDNA molecule encoding the antibody may be identified.

Other modulating agents include peptides, and nonpeptide mimetics thereof, that specifically interact with one or more regions of an ADAMTS polypeptide. Such agents may generally be identified using any well known binding assay, such as a representative assay provided herein. For example, such modulating agents may be isolated using well known techniques to screen substances from a variety of sources, such as plants, fungi or libraries of chemicals, small molecules or random peptides.

Other modulating agents may function by inhibiting or enhancing transcription or translation of an ADAMTS gene. For example, modulating agents may include antisense polynucleotides (DNA or RNA), which inhibit the transcription of a native ADAMTS protein. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. Antisense technology can generally be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (*see* Gee et al., *In* Huber and Carr, *Molecular and Immunologic Approaches*, Futura Publishing Co. (Mt. Kisco, NY; 1994). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes. Antisense polynucleotides are generally at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length.

Other agents may modulate transcription by interacting with an ADAMTS promoter. Such agents may be identified using standard assays, following isolation of an endogenous ADAMTS gene promoter region. One method for identifying a promoter region uses a PCR-based method to clone unknown genomic DNA sequences adjacent to a known cDNA sequence. This approach may generate a 5' flanking region, which may be subcloned and sequenced using standard methods. Primer extension and/or RNase protection analyses may be used to verify the transcriptional start site deduced from the cDNA.

To define the boundary of the promoter region, putative promoter inserts of varying sizes may be subcloned into a heterologous expression system containing a suitable reporter gene without a promoter or enhancer may be employed. Internal deletion constructs may be generated using unique internal restriction sites or by partial digestion of non-unique restriction sites. Constructs may then be transfected into cells that display high levels of ADAMTS protein expression In general, the construct with

the minimum 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter.

To evaluate the effect of a candidate agent on ADAMTS gene transcription, a promoter or regulatory element thereof may be operatively linked to a reporter gene. Such a construct may be transfected into a suitable host cell, which may be used to screen, for example, a combinatorial small molecule library. Briefly, cells are incubated with the library (*e.g.*, overnight). Cells are then lysed and the supernatant is analyzed for reporter gene activity according to standard protocols. Compounds that result in a decrease in reporter gene activity are inhibitors of ADAMTS gene transcription.

For modulating agents that act directly on an ADAMTS protein, an initial screen to assess the ability of candidate agents to bind to such a protein may be employed, although such binding is not essential for a modulating agent. For identifying agents that bind to an ADAMTS polypeptide, any of a variety of binding assays may be employed, such as standard affinity techniques and yeast two-hybrid screens. In general, the amount of candidate modulator added in such screens ranges from about 1 pM to 1 μM. An antibody or other modulating agent is said to "specifically bind" to an ADAMTS polypeptide if it reacts at a detectable level with such a polypeptide and does not react detectably with unrelated polypeptides. Such antibody binding properties may be assessed using, for example, an ELISA.

Screens for modulating agents that increase the rate of ADAMTS protein synthesis or stabilize ADAMTS protein may be readily performed using well known techniques that detect the level of ADAMTS protein or mRNA. Suitable assays include RNA protection assays, *in situ* hybridization, ELISAs, Northern blots and Western blots. Such assays may generally be performed using standard methods (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). For example, to detect mRNA encoding ADAMTS protein, a nucleic acid probe complementary to all or a portion of an ADAMTS gene sequence may be employed in a Northern blot analysis of mRNA prepared from suitable cells (*e.g.*, brain, lung, heart, spleen, spinal cord, testis, astrocytes or microglia).

To detect ADAMTS protein, a reagent that binds to the protein (typically an antibody) may be employed within an ELISA or Western assay. Following binding, a reporter group suitable for direct or indirect detection of the reagent is employed (*i.e.*, the reporter group may be covalently bound to the reagent or may be bound to a second molecule, such as Protein A, Protein G, immunoglobulin or lectin, which is itself capable of binding to the reagent). Suitable reporter groups include, but are not limited to, enzymes (*e.g.*, horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. Such reporter groups may be used to directly or indirectly detect binding of the reagent to a sample component using standard methods known to those of ordinary skill in the art.

To use such assays for identifying a modulating agent, the level of ADAMTS protein or mRNA is evaluated in cells (*e.g.*, astrocytes or microglia) treated with one or more candidate modulating agents. An increase or decrease in ADAMTS levels may be measured by evaluating ADAMTS mRNA and/or protein in the presence and absence of candidate modulating agent. In general, the amount of candidate modulator added in such screens ranges from about 1 pM to 1 μM. A candidate that results in a statistically significant change in the level of ADAMTS mRNA and/or protein is a modulating agent.

Modulating agents that decrease ADAMTS levels generally inhibit ADAMTS activity. To further evaluate the effect on ADAMTS activity, an assay may be performed as described above in the presence and absence of modulating agent. Agents that bind to a substrate of an ADAMTS protein domain may also be identified using such assays. Modulating agents may generally be administered by addition to a cell culture or by the methods described below for *in vivo* administration.

ADAMTS POLYPEPTIDE AND MODULATING AGENT MODIFICATION AND FORMULATIONS

An ADAMTS polypeptide or modulating agent as described herein may, but need not, be linked to one or more additional molecules. In particular, as discussed below, it may be beneficial for certain applications to link multiple polypeptides and/or modulating agents (which may, but need not, be identical) to a support material, such as

a polymeric matrix or a bead or other particle, which may be prepared from a variety of materials including glass, plastic or ceramics. For certain applications, biodegradable support materials are preferred.

Suitable methods for linking an ADAMTS polypeptide or modulating agent to a support material will depend upon the composition of the support and the intended use, and will be readily apparent to those of ordinary skill in the art. Attachment may generally be achieved through noncovalent association, such as adsorption or affinity or, preferably, via covalent attachment (which may be a direct linkage or may be a linkage by way of a cross-linking agent).

It may be beneficial for certain applications to link an ADAMTS polypeptide or modulating agent to a targeting agent to facilitate targeting to one or more specific tissues. As used herein, a "targeting agent," may be any substance (such as a compound or cell) that, when linked to a polypeptide or modulating agent enhances the transport of the polypeptide or modulating agent to a target tissue, thereby increasing the local concentration. Targeting agents include antibodies or fragments thereof, receptors, ligands and other molecules that bind to cells of, or in the vicinity of, the target tissue. Known targeting agents include serum hormones, antibodies against cell surface antigens, lectins, adhesion molecules, tumor cell surface binding ligands, steroids, cholesterol, lymphokines, fibrinolytic enzymes and those drugs and proteins that bind to a desired target site. An antibody targeting agent may be an intact (whole) molecule, a fragment thereof, or a functional equivalent thereof. Linkage is generally covalent and may be achieved by, for example, direct condensation or other reactions, or by way of bi- or multi-functional linkers. Within other embodiments, it may also be possible to target a polynucleotide encoding a polypeptide or modulating agent to a target tissue, thereby increasing the local concentration. Such targeting may be achieved using well known techniques, including retroviral and adenoviral infection. To treat a patient afflicted with certain conditions (*e.g.*, neurodegenerative conditions), it may be beneficial to deliver an ADAMTS polypeptide, polynucleotide or modulating agent to the intracellular space. Such targeting may be achieved using well known

techniques, such as through the use of polyethylene glycol or liposomes, as described in Turrens, *Xenobiotica 21*:1033-1040, 1991.

For certain embodiments, it may be beneficial to also, or alternatively, link a drug to a polypeptide or modulating agent. As used herein, the term "drug" refers to any bioactive agent intended for administration to a mammal to prevent or treat a disease or other undesirable condition.

Within certain aspects of the present invention, one or more polypeptides, polynucleotides or modulating agents as described herein may be present within a pharmaceutical composition or vaccine. A pharmaceutical composition further comprises one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants and liposomes.

To prepare a pharmaceutical composition, an effective amount of one or more polypeptides, polynucleotides and/or modulating agents is mixed with a suitable pharmaceutical carrier. Solutions or suspensions used for parenteral, intradermal, subcutaneous or topical application can include, for example, a sterile diluent (such as water), saline solution, fixed oil, polyethylene glycol, glycerin, propylene glycol or other synthetic solvent; antimicrobial agents (such as benzyl alcohol and methyl parabens); antioxidants (such as ascorbic acid and sodium bisulfite) and chelating agents (such as ethylenediaminetetraacetic acid (EDTA)); buffers (such as acetates, citrates and phosphates). If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, polypropylene glycol and mixtures thereof. In addition, other pharmaceutically active ingredients and/or suitable excipients such as salts, buffers and stabilizers may, but need not, be present within the composition.

A pharmaceutical composition is generally formulated and administered to exert a therapeutically useful effect while minimizing undesirable side effects. The

number and degree of acceptable side effects depend upon the condition for which the composition is administered. For example, certain toxic and undesirable side effects that are tolerated when treating life-threatening illnesses, such as tumors, would not be tolerated when treating disorders of lesser consequence. The concentration of active component in the composition will depend on absorption, inactivation and excretion rates thereof, the dosage schedule and the amount administered, as well as other factors that may be readily determined by those of skill in the art.

A polypeptide, polynucleotide or modulating agent may be prepared with carriers that protect it against rapid elimination from the body, such as time release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others known to those of ordinary skill in the art. Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polynucleotide, polypeptide or modulating agent dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Preferably the formulation provides a relatively constant level of modulating agent release. The amount of active component contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Pharmaceutical compositions of the present invention may be administered in a manner appropriate to the disease to be treated (or prevented). Administration may be effected by incubation of cells *ex vivo* or *in vivo*, such as by topical treatment, delivery by specific carrier or by vascular supply. Appropriate dosages and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease and the method of administration. In general, an appropriate dosage and treatment regimen provides the polypeptide, polynucleotide and/or modulating agent(s) in an

amount sufficient to provide therapeutic and/or prophylactic benefit (*i.e.*, an amount that ameliorates the symptoms or treats or delays or prevents progression of the condition). The precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by testing the compositions in model systems known in the art and extrapolating therefrom. Dosages may also vary with the severity of the condition to be alleviated. The composition may be administered one time, or may be divided into a number of smaller doses to be administered at intervals of time. In general, the use of the minimum dosage that is sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those of ordinary skill in the art, and for any particular subject, specific dosage regimens may be adjusted over time according to the individual need.

For pharmaceutical compositions comprising polynucleotides, the polynucleotide may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid, bacterial and viral expression systems, and colloidal dispersion systems such as liposomes. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal, as described above). The DNA may also be "naked," as described, for example, in Ulmer et al., *Science 259*:1745-1749, 1993.

Various viral vectors that can be used to introduce a nucleic acid sequence into the targeted patient's cells include, but are not limited to, vaccinia or other pox virus, herpes virus, retrovirus, or adenovirus. Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. Preferably, the retroviral vector is a derivative of a murine or avian retrovirus including, but not limited to, Moloney murine leukemia virus (MoMuLV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), and Rous Sarcoma Virus (RSV). A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a gene that

encodes the ligand for a receptor on a specific target cell (to render the vector target specific).

Viral vectors are typically non-pathogenic (defective), replication competent viruses, which require assistance in order to produce infectious vector particles. This assistance can be provided, for example, by using helper cell lines that contain plasmids that encode all of the structural genes of the retrovirus under the control of regulatory sequences within the LTR, but that are missing a nucleotide sequence which enables the packaging mechanism to recognize an RNA transcript for encapsulation. Such helper cell lines include (but are not limited to) Ψ2, PA317 and PA12. A retroviral vector introduced into such cells can be packaged and vector virion produced. The vector virions produced by this method can then be used to infect a tissue cell line, such as NIH 3T3 cells, to produce large quantities of chimeric retroviral virions.

Another targeted delivery system for polynucleotides is a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). RNA, DNA and intact virions can be encapsulated within the aqueous interior and delivered to cells in a biologically active form. The preparation and use of liposomes is well known to those of ordinary skill in the art.

THERAPEUTIC APPLICATIONS

As noted above, ADAMTS polynucleotides, polypeptides and modulating agents may generally be used for the therapy of diseases characterized by neuroinflammation or neurodegeneration. In general, ADAMTS metalloproteinases are believed to function in cleaving proteins from cell surfaces (which may be surfaces of cells that synthesize the metalloproteinase or other cells). Pharmaceutical compositions as provided herein may be administered to a patient, alone or in combination with other therapies, to treat or prevent neurodegenerative diseases such as Alzheimer's disease,

Parkinson's disease or stroke. Pharmaceutical compositions provided herein may also be beneficial for therapy of conditions related to cell proliferation, cell migration, inflammation or angiogenesis. Such conditions include cancer, arthritis and autoimmune diseases.

Modulation of an ADAMTS function, either *in vitro* or *in vivo*, may generally be achieved by administering a modulating agent that inhibits ADAMTS transcription, translation or activity. In some instances, however, the ADAMTS activity may be lower than is desired. In such cases, polynucleotides, polypeptides and/or modulating agents that enhance ADAMTS activity may be administered. The activity of an endogenous ADAMTS protein within a cell may be increased by, for example, inducing expression of the ADAMTS gene and/or administering a modulating agent that enhances ADAMTS activity. Each of these methods may be performed using mammalian cells in culture or within a mammal, such as a human.

Certain ADAMTS polypeptides may be used to cleave the proteoglycan brevican. Brevican is a brain specific proteoglycan. The secreted form of brevican is upregulated in response to CNS injury and has been implicated in reactive gliosis, and a cleaved form may be important for tumor invasion (*see* Zhang et al., *J. Neuroscience* *18*:2370-76, 1998). Thus, brevican cleavage appears to be important in brain injury and gliomas. Modulating agents that inhibit the ability of such ADAMTS polypeptides to cleave brevican may be used to treat brain injuries, brain tumors and other invasive tumors.

Routes and frequency of administration, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. A suitable dose is an amount of a compound that, when administered as described above, is capable of causing modulation of an ADAMTS activity that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, an appropriate dosage and treatment regimen

provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. In general, suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

DIAGNOSTIC APPLICATIONS

In a related aspect of the present invention, kits for detecting ADAMTS proteins are provided. Such kits may be designed for detecting the level of ADAMTS protein or nucleic acid encoding an ADAMTS protein within a sample. In general, the kits of the present invention comprise one or more containers enclosing elements, such as reagents or buffers, to be used in the assay. A kit for detecting the level of ADAMTS protein or nucleic acid typically contains a reagent that binds to the ADAMTS protein, DNA or RNA. To detect nucleic acid, the reagent may be a nucleic acid probe or a PCR primer. To detect protein, the reagent is typically an antibody. A kit may also contain a reporter group suitable for direct or indirect detection of the reagent as described above.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

Preparation of Novel ADAMTS Family Members

This Example illustrates the cloning of cDNA molecules encoding members of the ADAMTS family of metalloproteinases based on induction of expression in rat glial cells by aggregated beta amyloid.

Subtractive hybridization was performed as described (Kelner and Maki. *Methods in Molecular Medicine, vol 22: Neurodegeneration Methods and Protocols*, Eds J. Harry and H.A. Tilson, Human Press Inc., Totowa, NJ). Briefly, rat glial cells were cultured and treated with aggregated beta amyloid. After 24 hours, RNA was prepared from these cells and from control cells that were not treated with beta amyloid. Genes expressed in the activated cells but not the control cells were sequenced. This screen identified rat ADAMTS-3 (cDNA and encoded protein sequences shown in Figure 26 (SEQ ID NO:25) and Figure 27 (SEQ ID NO:26), respectively). The rat cDNA was used to screen a human cDNA library and resulted in the isolation of human ADAMTS-3. ADAMTS-3 is 2,866 nucleotides in length (Figures 9A and 9B; SEQ ID NO:9) and codes for a putative protein that is 955 amino acids in length (Figure 10; SEQ ID NO:10). ADAMTS-3 contains a metalloproteinase domain, a disintegrin domain, thrombospondin motifs and an ECM domain.

Example 2

Preparation of Novel ADAMTS Family Members using Degenerate PCR

This Example illustrates the use of degenerate PCR to clone partial cDNA molecules encoding members of the ADAMTS family of metalloproteinases.

PCR was performed using rat microglia cDNA and degenerate oligonucleotides derived from an analysis of the sequence from ADAMTS-1 and ADAMTS-3. Degenerate primers were designed based on common sequences between

these two genes. The original degenerate primers were designed based on a small region of these two genes that was cloned. One primer had the sequence 5'-TTYMGNGARGARCARTGY-3' (SEQ ID NO:33), while the other primer had the sequence 5'-RCANAYNCCRCAYTTRTC-3' (SEQ ID NO:34). The PCR conditions were annealing at 47°C for 1 minute, 72°C extension for 2 minutes and 94°C denaturation for 30 seconds.

Following PCR samples were fractionated by gel electrophoresis and fragments of the expected size were cloned into the vector pCRScript and sequenced. One amplified cDNA molecule was designated rat ADAMTS-2 (Figure 24; SEQ ID NO:23), and the encoded protein has the predicted sequence shown in Figure 25 (SEQ ID NO:24). This cDNA was used to screen a human cDNA library, from which human ADAMTS-2 was identified. Human ADAMTS-2 has the sequence shown in Figure 1 (SEQ ID NO:1), and appears to encode the protein recited in Figure 2 (SEQ ID NO:2).

Rat ADAMTS-4 was isolated using the PCR approach and is a polynucleotide having the sequence shown in Figures 3A and 3B (SEQ ID NO:3), which appears to encode the protein recited in Figure 4 (SEQ ID NO:4). For rat ADAMTS-4 the metalloproteinase domain begins at amino acid 260(R), the disintegrin domain begins at residue 487(Q), a thrombospondin motif begins at residue 570(W) and an ECM domain begins at residue 621(C). The rat ADAMTS-4 sequence was used to screen a human cDNA library and human ADAMTS-4 was isolated. Human ADAMTS-4 is 1455 nucleotides in length (Figure 15; SEQ ID NO:15) and codes for a putative protein that is 485 amino acids in length (Figure 16; SEQ ID NO:16). The disintegrin domain in human ADAMTS-4 begins at amino acid 39(E), the start of the first thrombospondin repeat is at amino acid 124(W) and the start of another thrombospondin repeat is at amino acid 479(C). Bovine ADAMTS-4 cDNA has the sequence shown in Figure 18 (SEQ ID NO:17), encoding the predicted amino acid sequence shown in Figure 19 (SEQ ID NO:18).

Rat ADAMTS-5 is a cDNA molecule with the sequence shown in Figure 13 (SEQ ID NO:13), encoding the amino acid sequence shown in Figure 14 (SEQ ID

NO:14). The human ADAMTS cDNA and protein sequences are shown in Figure 22 (SEQ ID NO:21) and Figure 23 (SEQ ID NO:22), respectively.

ADAMTS-4 was further shown to cleave the brain-specific proteoglycan brevican. Five hundred micrograms of purified brevican was cleaved with 500 micrograms of human ADAMTS-4 and incubated overnight at 37°C. The cleavage reaction was vacuum dried and resuspended in SDS sample loading dye for running on a 4-20% SDS polyacrylamide gel. Equal amounts of cleaved and uncleaved brevican were added to the gel. After electrophoresis the gel was stained with Coumassie Blue to visualize the protein bands. The results, presented in Figure 30, show that brevican is cleaved upon incubation with ADAMTS-4.

Example 3

Identification of ADAMTS Family Members using Database Searches

This Example illustrates the use of database searches to identify cDNA molecules encoding members of the ADAMTS family of metalloproteinases.

To identify additional members of the ADAMTS family, the GenBank database was searched for sequences similar to ADAMTS-1 and ADAMTS-3. This search retrieved KIAA0605 (Figures 5A and 5B; SEQ ID NO:5), which appears to encode a protein of 951 amino acids (Figure 6; SEQ ID NO:6). The coding sequence contains thrombospondin motifs, but no metalloproteinase or disintegrin domains have been identified. A thrombospondin motif begins with amino acid 50(W). Six additional thrombospondin motifs were found beginning with amino acid 568(K). The domain that binds to the extracellular matrix begins with amino acid 105(C).

Also retrieved was KIAA0366 (Figures 7A and 7B; SEQ ID NO:7), which appears to encode a protein of 951 amino acids (Figure 8; SEQ ID NO:8), including metalloproteinase and disintegrin domains, as well as thrombospondin motifs. For KIAA0366, the metalloproteinase domain begins with amino acid 241(T), the disintegrin domain begins with amino acid 460(D), a thrombospondin domain is present beginning at position 544(W) and another thrombospondin repeat occurs at position

842(W). The ECM domain begins at amino acid 597(C) and contains the semiconserved sequence FREEQC (SEQ ID NO:32). KIAA0366 does not appear to have a transmembrane domain, and therefore is likely to encode a secreted protein.

An additional sequence identified in this search was KIAA0688 (Figures 11A and 11B; SEQ ID NO:11), which appears to encode the protein shown in Figure 12 and SEQ ID NO:12. This gene codes for a protein with a metalloproteinase domain beginning at amino acid 245(R), a disintegrin domain beginning at amino acid 465(E), a thrombospondin motif at position 550(W), an ECM domain at position 601(C) and two additional thrombospondin motifs at position 905(W). A bovine KIAA0688 cDNA sequence is shown in Figure 20 (SEQ ID NO:19), and the predicted amino acid sequence of the encoded protein is shown in Figure 21 (SEQ ID NO:20).

Figures 17A-17G present an alignment of the ADAMTS protein sequences described herein, along with ADAMTS-1.

Example 4

Identification and Characterization of ADAMTS-9

This Example illustrates the cloning and characterization of the ADAM-TS/metallospondin family member designated herein as ADAMTS-9.

A small fragment of the rat ADAMTS-9 gene was initially cloned from a beta amyloid-treated (35 μg/ml aggregated Aβ 1-42) rat astrocyte cDNA library. DNA sequence analysis was performed using a PCR procedure employing fluorescent dideoxynucleotides and a model ABI-377 automated sequencer (PE Biosystem). BLAST sequence analysis revealed low homology at the protein level to the spacer region of the murine ADAMTS-1 gene.

This clone was labeled with [α-^{32}P]dCTP using the Prime It II kit (Stratagene) and used to screen a human spinal cord phage library (Clontech) according to the manufacturer's instructions. Positive plaques were purified and lambda DNA prepared (Qiagen). Several overlapping clones were sequenced that had homology to the original rat clone. In order to determine the 5′ and 3′ ends of the gene RACE (rapid

amplification of cDNA ends) analysis was performed using Marathon Ready placenta and fetal cDNA libraries (Clontech) with SMART primers (Clontech). Overlapping sequence was used to confirm the full length clone. The full length protein sequence of human ADAMTS-9 is shown in Figure 29. The 5′ end of the clone contains a methionine codon within a good Kozak consensus for translation initiation. A signal peptide sequence is located just downstream of this methionine in the translated ORF, and the size of the pro-domain is similar to that of other ADAM-TS family members. Therefore, this appears to be the starting methionine of ADAMTS-9.

The overall protein sequence of ADAMTS-9 is similar to that of the other ADAM-TS proteins. All of these family members have a pro-domain, metalloprotease domain, disintegrin-like domain, thrombospondin domain, spacer region, and a variable number of a thrombospondin-like submotifs at the carboxyl-terminal end of the protein (Figure 32A). Like other ADAM-TS family members, ADAMTS 9 contains an amino-terminal signal peptide sequence and lacks a transmembrane domain.

Among the 23 ADAM family members, 10 are predicted to be active proteases based on the sequence of their Zn binding catalytic sites (Black and White, *Curr. Opin. Cell. Biol 10*:654-659, 1998). The consensus catalytic sequence site based on ADAM and snake venom metalloproteases is HE*X*GH*XX*G*XX*HD (SEQ ID NO:51). The ADAM-TS family of proteins has homology to this consensus sequence except at the second conserved glycine. ADAMTS 9 has an asparagine at this conserved glycine site in the helix. Two other ADAM-TS proteins, ADAMTS-1 and ADAMTS-4, also have an asparagine in this position instead of glycine (Figure 32B). This suggests that ADAMTS-9, line ADAMTS-1 and ADAMTS-4, may have an active metalloprotease domain.

It has been proposed that an invarient cysteine residue in the pro-domain of MMP and ADAM proteins coordinates the catalytic Zn ion in the metalloprotease domain, thus maintaining the protease in an inactive state (Loechel et al., J. Biol Chem. 274:13427-33, 1999). Once the pro-domain is cleaved this interaction is interrupted and the protease is activated by a "cysteine switch" mechanism. A proposed cysteine switch

residue in ADAMTS-9 is marked in Figure 29 by a star. Proteolytic processing of the pro-domain of ADAM and ADAM-TS proteins is believed to occur by furin endopeptidases in the Golgi. ADAMTS-9 contains two potential furin cleavage sites (consensus R*X*(K/R)R; SEQ ID NO:35) at the end of the pro-domain (see Figure 29). Based on the sequence of mature murine *ADAMTS-1*, the second furin cleavage site is most likely used in ADAMTS-9 (resulting amino-terminus FLSYPR).

Following the metalloprotease domain, ADAMTS-9 contains a cysteine-rich region that has homology to the disintegrin domain in snake venom metalloprotease and ADAMs. Next, all of the ADAM-TS family members contain an internal TSP1 motif that has the two conserved heparin binding segments: W(S/G)*X*WS*X*W (SEQ ID NO:36) and CSVTCG (SEQ ID NO:37). Separating the internal TSP1 motif and the carboxy terminal TSP1-like submotifs is a variable length spacer region. As seen in Figure 32A, most ADAM-TS family members have between one and three TSP1-like submotifs at the end of the protein. However at the extremes are ADAMTS 3 which has no TSP1-like motifs and *C. elegans* GON-1 which has 17 of these motifs. ADAMTS-9 contains one internal TSP1 motif and three TSP-1 like submotifs at the carboxyl end (Figure 30A). A possible role for ADAMTS 9 in the adult is suppression of angiogenesis through the carboxy-terminal TSP1 motifs.

Overall, the predicted mature forms of the ADAM-TS proteins show 20-40% similarity to each other. Interestingly, by BLAST analysis ADAMTS-9 shows as much homology to *C. elegans* GON-1 as to other human ADAM-TS, suggesting that ADAMTS 9 may be the human homologue of GON-1. The dendrogram in Figure 30C (prepared with the MegAlign program (DNAStar)) shows the relationship between the known human ADAM-TS members, ADAMTS 9, and GON-1.

The expression pattern of ADAMTS 9 was examined in a variety of human adult and fetal tissues using RT-PCR. For tissue distribution analysis, human multiple tissue cDNA panels I and II were purchased from Clontech. RT-PCR was performed using a touchdown procedure where the annealing temperature was dropped from 63°C to 57°C over 10 cycles then kept at 57°C for 20 cycles. The sense primer was CAGGGGAAACAGACGATGACAACT (SEQ ID NO:38) and the antisense

primer was TGCGGTAACCCAAGCCACACT (SEQ ID NO:39). Expected product size was 510 bp. Control primers to glyceraldehyde-3-phosphate dehydrogenase (G3PDH) were supplied by Clontech--expected size is about 1 kb.

As seen with other ADAM-TS genes, Northern blot analysis showed very low levels of expression. Therefore a more sensitive RT-PCR procedure was used. The cDNA panels used were normalized to the mRNA expression levels of several different housekeeping genes to ensure accurate assessment of tissue specificity. ADAMTS-9 was found in ovary, pancreas, heart, kidney, lung, placenta, and strikingly in all fetal tissues examined (Figure 31), suggesting a possible role in development. In addition, using hybridization to cDNA libraries we have identified ADAMTS-9 in adult spinal cord and brain. However, ADAMTS-9 was not detected in colon, leukocyte, prostate, small intestine, testis, liver, skeletal muscle, spleen or thymus (Figure 31). Expression of the G3PDH housekeeping gene in all cDNAs tested is shown as a control for template integrity and the RT-PCR procedure. One notable difference in the expression pattern of ADAMTS-9 compared to other ADAMTS genes is the presence of ADAMTS-9 in the adult kidney. This is of interest since the chromosomal locus containing ADAMTS-9 is often deleted in renal tumors.

A genomic clone of ADAMTS 9 was obtained by screening a human P1 library and used for FISH analysis (Genome Systems). Briefly, the human ADAMTS-9 genomic clone was labeled with digoxigenin dUTP by nick translation. Labeled probe was combined with sheared human DNA and hybridized to normal metaphase chromosomes derived from PHA stimulated peripheral blood lymphocites in a solution containing 50% formamide, 10% dextran sulfate and 2X SSC. Specific hybridization signals were detected by incubating the hybridized slides in fluoresceinated antidigoxigenin antibodies followed by counterstaining with DAPI for one-color experiments. Probe detection for two-color experiments was accomplished by incubating the slides in fluoresceinated antidigoxigenin antibodies and Texas red avidin followed by counterstaining with DAPI. A total of 80 metaphase cells were analyzed with 70 exhibiting specific labeling. Initial FISH experiments resulted in specific labeling of the short arm of chromosome 3. Measurement of 10 specifically labeled

chromosome 3's demonstrated that ADAMTS-9 is located at a position which is 30% the distance from the centromere to the telomere of chromosome arm 3p, an area which corresponds to 3p14.3-21.1 (Figures 32A and 32B). Since deletions and other rearrangements of this locus are frequent and early events in the pathogenesis of a number of human cancers (including renal cell carcinoma, breast cancers, uterine cervical carcinoma and vulvar carcinomas, this region may contain one or more tumor suppressor genes.

The chromosomal localization of the human ADAMTS 9 locus was independently confirmed by PCR analysis of the Stanford G3 radiation hybrid mapping panel. The G3 hybrid mapping panel (Stewart et al., *Genomic Res.* 7:422-433, 1997) containing 83 radiation hybrid DNA, as well as human and hamster control DNAs was obtained from Research genetics Inc. (Huntsville, Alabama). The human chromosome content of each somatic cell hybrid was established by the Stanford Human Genome Center using more than 10,000 STSs derived from random genetic markers and expressed tagged sequences (http://www-shgc.stanford.edu/Mapping/rh/). PCR reactions were carried out in a 10 μl reaction volume containing 25 ng DNA template, 25 μm deoxynucleotide triphosphates, 20 pmol of each oligonucleotide primer, 0.5 U of Taq polymerase (Boehringer Mannheim), 2.5 mM $MgCl_2$, 50 mM KCl and 10 mM Tris-HCl (pH 8.3). The sense primer is GTGCGCTGGGTCCCTAAATAC (SEQ ID NO:40) which is in the coding sequence and the antisense primer is AAAATCACAGGTTGGCAGCGG (SEQ ID NO:41) which is in an intronic sequence. Thirty cycles of PCR were performed. Ten cycles consisted of denaturing at 94°C for 15 seconds, annealing at 62°C for 30 seconds, going down 0.5°C each cycle and extension at 72°C for 30 seconds. Twenty more cycles were performed using the same denaturing and extension conditions and keeping the annealing at 57°C for 30 seconds. PCR was proceeded by a 2 min incubation at 94°C and followed by a 72°C final soak for 10 minutes. Amplified products were electrophoresed through a 2% agarose gel and visualized by ethidium bromide staining. The resulting PCR product was a 302 bp human specific fragment. The presence or absence of the ADAMTS 9 product was scored for each of the somatic cell hybrids. The results were submitted to the Stanford

Radiation Hybrid Server via the internet (http://www-shgc.stanford.edu) and the completed data were returned to us. ADAMTS 9 was linked to the ordered markers SHGC-33668 with a LOD score of 11.47 and SHGC-20118 (D3S3571) with a LOD score of 11.06. The results confirm localization of ADAMTS 9 to the short arm of chromosome 3 and place ADAMTS-9 within the context of established maps. Furthermore SHGC-20118 (D3S3571) has been mapped to 3p14.2, placing ADAMTS-9 closer to the 14.2-14.3 region of chromosome 3. This location is interesting in that it contains a well characterized breakpoint for translocations common in hereditary renal cell carcinomas.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

CLAIMS

1. An isolated polynucleotide that encodes an ADAMTS polypeptide. wherein the polypeptide comprises:

(a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or

(b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.

2. A polynucleotide according to claim 1, wherein the polynucleotide comprises a sequence recited in any one of SEQ ID NOs:1, 3, 9, 13, 15, 17, 21, 23 or 25.

3. A polynucleotide according to claim 1, wherein substitutions, if any, are present at no more than 5% of the consecutive residues of the ADAMTS protein.

4. A polynucleotide according to claim 1, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.

5. A recombinant expression vector comprising a polynucleotide according to claim 1.

6. A host cell transformed or transfected with an expression vector according to claim 5.

7. An isolated antisense polynucleotide complementary to at least 20 consecutive nucleotides present within a polynucleotide according to claim 1.

8. A method for preparing an ADAMTS polypeptide, the method comprising:

(a) culturing a host cell transformed or transfected with an expression vector comprising a polynucleotide that encodes an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the step of culturing is performed under conditions promoting expression of the polynucleotide sequence; and

(b) recovering an ADAMTS polypeptide.

9. A method for preparing an ADAMTS polypeptide, the method comprising:

(a) culturing a host cell according to claim 6 under conditions promoting expression of the polynucleotide; and

(b) recovering an ADAMTS polypeptide.

10. An isolated ADAMTS polypeptide comprising:

(a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or

(b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.

11. An ADAMTS polypeptide according to claim 10, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.

12. A polypeptide comprising an amino acid sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27.

13. An isolated ADAMTS polypeptide comprising:

(a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20

(b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.

14. An ADAMTS polypeptide according to claim 13, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.

15. An ADAMTS polypeptide according to claim 13, wherein the polypeptide comprises at least 40 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20.

16. A polypeptide comprising an amino acid sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20.

17. A pharmaceutical composition comprising:

(a) an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) a physiologically acceptable carrier.

18. A vaccine comprising:

(a) an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22. 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) a non-specific immune response enhancer.

19. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to an ADAMTS polypeptide that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

20. A method for screening for an agent that modulates ADAMTS protein expression in a cell, comprising:

(a) contacting a candidate modulator with a cell expressing an ADAMTS polypeptide, wherein the polypeptide comprises:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12. 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein

substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) subsequently evaluating the effect of the candidate modulator on expression of an ADAMTS mRNA or polypeptide, and therefrom identifying an agent that modulates ADAMTS protein expression in the cell.

21. A method for screening for an agent that modulates an ADAMTS protein activity, comprising:

(a) contacting a candidate modulator with an ADAMTS polypeptide, comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein;

and wherein the step of contacting is carried out under conditions and for a time sufficient to allow the candidate modulator to interact with the polypeptide; and

(b) subsequently evaluating the effect of the candidate modulator on an ADAMTS activity of the polypeptide, and therefrom identifying an agent that modulates an activity of an ADAMTS protein.

22. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for inhibiting neuroinflammation in a patient.

23. An agent according to claim 22, wherein ADAMTS activity is decreased by inhibiting expression of an endogenous ADAMTS gene.

24. An agent according to claim 22, wherein ADAMTS activity is decreased by administering a modulating agent that binds to an ADAMTS protein.

25. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for inhibiting neurodegeneration in a patient.

26. An agent according to claim 25, wherein ADAMTS activity is decreased by inhibiting expression of an endogenous ADAMTS gene.

27. An agent according to claim 25, wherein ADAMTS activity is decreased by administering a modulating agent that binds to an ADAMTS protein.

28. A pharmaceutical composition according to claim 17, for use in the manufacture of a medicament for method for treating a patient afflicted with a condition associated with neuroinflammation and/or neurodegeneration.

29. A composition according to claim 28, wherein the condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease and stroke.

30. A method for modulating ADAMTS activity in a cell, comprising contacting a cell expressing an ADAMTS polypeptide with an effective amount of an agent that modulates ADAMTS protein activity or expression, wherein the ADAMTS polypeptide comprises:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein;

and thereby modulating ADAMTS activity in the cell.

31. A pharmaceutical composition according to claim 17, for use in the manufacture of a medicament for treating a patient afflicted with a condition associated with cell proliferation, cell migration, inflammation and/or angiogenesis.

32. A composition according to claim 31, wherein the condition is selected from the group consisting of cancer, arthritis and autoimmune diseases.

33. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with an invasive tumor.

34. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with a brain tumor.

35. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20,

22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with a brain injury.

36. An agent according to any one of claims 33-35, wherein the ADAMTS protein comprises a sequence recited in SEQ ID NO:16.

AGGACCAAGCGGTTTGTGTCTGAGGCGCGCTTCGTGGAGACGCTGCTGGTGGCCGATGCGTCCATGGCTGCCTTCTACGG
GGCCGACCTGCAGAACCACATCCTGACGTTAATGTCTGTGGCAGCCCGAATCTACAAGCACCCCAGCATCAAGAATTCCA
TCAACCTGATGGTGGTAAAAGTGCTGATCGTAGAAGATGAAAAATGGGGCCCAGAGGTGTCCGACAATGGGGGGCTTACA
CTGCGTAACTTCTGCAACTGGCAGCGGCGTTTCAACCAGCCCAGCGACCGGCACCCAGAGCACTACGACACGGCCATCCT
GCTCACCAGACAGAACTTCTGTGGGCAGGAGGGGCTGTGTGACACCCTGGGTGTGGCAGACATCGGGACCATTTGTGACC
CCAACAAAAGCTGCTCCGTGATCGAGGATGAGGGGCTCCAGGCGGCCCACACCCTGGCCCATGAACTAGGGCACGTCCTC
AGCATGCCCCACGACGACTCCAAGCCCTGCACACGGCTCTTCGGGCCCATGGGCAAGCACCACGTGATGGCACCGCTGTT
CGTCCACCTGAACCAGACGCTGCCCTGGTCCCCCTGCAGCGCCATGTATCTCACAGAGCTTCTGGACGGCGGGCACGGAG
ACTGTCTCCTGGATGCCCCTGCTGCGGCCCTGCCCCTCCCCACAGGCCTCCCGGGCCGCATGGCCCTGTACCAGCTGGAC
CAGCAGTGCAGGCAGATCTTTGGGCCGGATTTCCGCCACTGCCCCAACACCTCTGCTCAGGACGTCTGCGCCCAGCTTTG
GTGCCACACTGATGGGGCTGAGCCCCTGTGCCACACGAAGAATGGCAGCCTGCCCTGGGCTGACGGCACGCCGTGCGGGC
CTGGGCACCTCTGCTCAGAAGGCAGCTGTCTACCTGAGGAGGAAGTGGAGAGGCCCAAGCCCGTGGTAGATGGAGGCTGG
GCACCGTGGGGACCCTGGGGAGAATGTTCTCGGACCTGTGGAGGAGGAGTACAGTTTTCACACCGTGAGTGCAAGGACCC
CGAGCCTCAGAATGGAGGAAGATACTGCCTGGGTCGGAGAGCCAAGTACCAGTCATGCCACACGGAGGAATGCCCCCCTG
ACGGGAAAAGCTTCAGGGAGCAGCAGTGTGAGAAGTATAATGCCTACAATTACACTGACATGGACGGGAATCTCCTGCAG
TGGGTCCCCAAGTATGCTGGGGTGTCCCCCCGGGACCGCTGCAAGTTGTTCTGCCGAGCCCGGGGGAGGAGCGAGTTCAA
AGTGTTCGAGGCCAAGGTGATTGATGGCACCCTGTGTGGGCCAGAAACACTGGCCATCTGTGTCCGTGGCCAGTGTGTCA
AGGCCGGCTGTGACCATGTGGTGGACTCGTTTTGGAAGCTGGACAAATGCGGGGTGTGTGGGGGGAAAGGCAACTCCTGC
AGGAAGGGCTCCGGGTCCCTCACCCCCACCAATTATGGCTACAATGACATTGTCACCATCCCAGCTGGTGCCACTAATAT
TGACGTGAAGCAGCGGAGCCACCCGGGTGTGCAGAACGATGGGAACTACCTGGCGCTGAAGACGGCTGATGGGCAGTACC
TGCTCAACGGCAACCTGGCCATCTCTGCCATAGAGCAGGACATCTTGGTGAAGGGGACCATCCTGAAGTACAGCGGCTCC
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GGTCTTCCCCCCAAAAGTCAAATACACCTTCTTTGTTCCTAATGACGTGGACTTTAGCATGCAGAGCAGCAAAGAGAGAG
CAACCACCAACATCACCCAGCCGCTGCTCCACGCACAGTGGGTGCTGGGGGACTGGTCTGAGTGCTCTAGCACCTGCGGG
GCCGGCTGGCAGAGGCGAACTGTAGAGTGCAGGGACCCCTCCGGCCAGGCCTCTGCCACCTGCAACAAGGCTCTGAAACC
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GGCCTCCCATTGCCGCAACCCCTCCAGTACTGCACAAATTCCTAAGGGGGAAGAGGAGAGGGTATGGGGCGGCAGACCCT
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TACCAGACAGGACGCCCGCGAATTC

Fig. 1

RTKRFVSEARFVETLLVADASMAAFYGADLQNHILTLMSVAARIYKHPSIKNSINLMVVKVLIVEDEKWGPEVSDNGGLT
LRNFCNWQRRFNQPSDRHPEHYDTAILLTRQNFCGQEGLCDTLGVADIGTICDPNKSCSVIEDEGLQAAHTLAHELGHVL
SMPHDDSKPCTRLFGPMGKHHVMAPLFVHLNQTLPWSPCSAMYLTELLDGGHGDCLLDAPAAALPLPTGLPGRMALYQLD
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RKGSGSLTPTNYGYNDIVTIPAGATNIDVKQRSHPGVQNDGNYLALKTADGQYLLNGNLAISAIEQDILVKGTILKYSGS
IATLERLQSFRPLPEPLTVQLLAVPGEVFPPKVKYTFFVPNDVDFSMQSSKERATTNITQPLLHAQWVLGDWSECSSTCG
AGWQRRTVECRDPSGQASATCNKALKPEDAKPCESQLCPL.

Fig. 2

CCCCCCCTCGAGGTCGACGGTATCGATAAGCTTGATATCGAATTCCGGGCCCCCCACCCCCGCCCCTGAAACTTCTATAG
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Fig. 3A

TGTACAAAGATTATCGGAACCTTCAATAAAAAAAGCAAGGGTTATACTGACGTTGTGAGGATCCCTGAAGGAGCAACCCA
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AGACCCAACTAAAGCATTAGACGTCCGTTACAGCTTTTTTGTTCCCAAGAAGACCACTCAAAAAGTGAATTCCTGCAGCC
CGGGGGATCCACTAGTTCTAGAGCGGCCG

Fig. 3B

MRLEWASLLLLLLLLCASCLALAADNPAAAPAQDKTRQPRAAAAAAQPDQRQWEETQERGHLQPLARQRRSSGLVQNIDQ
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CGGDNSSCTKIIGTFNKKSKGYTDVVRIPEGATHIKVRQFKAXDQTRFTAYLALKKKTGEYLINGKYMISTSETIIDING
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Fig. 4

KIAA0605 Accession #: AB011177

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Fig. 5A

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```

Fig. 5B

```
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```

Fig. 6

DNA sequence of metalloproteinase gene (KIAA0366) Accession #: AB002364

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```

Fig. 7A

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agaaaaatat gttgctaaga ttgtgttggt cgctctctga agcagaaaag ggactggaac 3900
caattgtgca tatcagctga ctttttgttt gttttagaaa agttacagta aaaattaaaa 3960
agagatacca atggtttaca ctttaacaag aaattttgga tatggaacaa agaattctta 4020
gacttgtatt cctatttatc tatattagaa atattgtatg agcaaatttg cagctgttgt 4080
gtaaatactg tatattgcaa aaatcagtat tattttaaga gatgtgttct caaatgattg 4140
tttactatat tacatttctg gatgttctag gtgcctgtcg ttgagtattg ccttgtttga 4200
cattctatag gttaattttc aaagcagagt attacaaaag agaagttaga attacagcta 4260
ctgacaatat aaagggtttt gttgaatcaa caatgtgata cgtaaattat agaaaaagaa 4320
aagaaacaca aaagctatag atatacagat atcagcttac ctattgcctt ctatacttat 4380
aatttaaagg attggtgtct tagtacactt gtggtcacag ggatcaacga atagtaaata 4440
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ggtgtccttt gtttttgtgt gtgtgtgttc ttttttaatt ttcgcattgt tgacagatac 4560
aaacagttat actcaatgta ctgtaataat cgcaaaggaa aaagttttgg gataacttat 4620
ttgtatgttg gtagctgaga aaaatatcat cagtctagaa ttgatatttg agtatagtag 4680
agctttgggg ctttgaaggc aggttcaaga aagcatatgt cgatggttga gatatttatt 4740
ttccatatgg ttcatgttca aatgttcaca accacaatgc atctgactgc aataatgtgc 4800
taataattta tgtcagtagt caccttgctc acagcaaagc cagaaatgct ctctccaggg 4860
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tttttttctt tgatagtatt tttatgtact aaatatttac actaatatca attacatatt 4980
ttggtaaact agagagacat aattagagat gcatgctttg ttctgtgcat agagaccttt 5040
aagcaaacta ctacagccaa ctcaaaagct aaaactgaac aaatttgatg ttatgcaaac 5100
atcttgcatt tttagtagtt gatattaagt tgatgacttg tttcccttca aggaaacatt 5160

Fig. 7B

```
aaattgtatg gactcagcta gctgttcaat gaaattgtga attagaaaca tttttaaaag     5220
tttttgaaag agataagtgc atcatgaatt acatgtacat gagaggagat agtgatatca     5280
gcataatgat tttgaggtca gtacctgagc tgtctaaaaa tatattatac aaactaaaat     5340
gtagatgaat taacctctca aagcacagaa tgtgcaagaa cttttgcatt ttaatcgttg     5400
taaactaaca gcttaaacta ttgactctat acctctaaag aattgctgct actttgtgca     5460
agaactttga aggtcaaatt aggcaaattc cagatagtaa aacaatccct aagccttaag     5520
tctttttttt ttcctaaaaa ttcccataga ataaaattct ctctagttta cttgtgtgtg     5580
catacatctc atccacaggg gaagataaag atggtcacac aaacagtttc cataaagatg     5640
tacatattca ttatacttct gacctttggg ctttcttttc tactaagcta aaaattcctt     5700
tttatcaaag tgtacactac tgatgctgtt tgttgtactg agagcacgta ccaataaaaa     5760
tgttaacaaa atat                                                       5774
```

Fig. 7C

```
1                                                                              80
slwliaaalvevrtsadgqagneemvqidlpikryreyeivtpvstnlegrylshtlsashkkrsardvssnpeqlffni
tafgkdfhlrlkpntqlvapgavvewhetslvpgnitdpinnhqpgsatyrirktepiqtncayvgdivdipgtsvaisn
cdglagmiksdneeyfieplergkqmeeekgrihvvykrsaveqapidmskdfhyresdlegldd lgtvygnihqqlnet
mrrrrhagendynievllgvddsvvrfhgkehvqnylltlmnivneiyhdeslgvhinvvlvrmimlgyaksisliergn
psrslenvcrwasqqqrsdlnhsehhdhaifltrqdfgpagmqgyapvtgmchpvrsctlnhedgfssafvvahetghvl
gmehdgqgnrcgdetamgsvmaplvqaafhryhwsrcsgqelkryinsydclldd pfdhdwpklpelpginysmdeqcrf
dfgvgykmctafrtfdpckqlwcshpdnpyfcktkkgppldgtecaagkwcykghcmwknanqqkqdgnwgswtkfgscs
rtcgtgvrfrtrqcnnpmpinggqdcpgvnfeyqlcnteecqkhfedfraqqcqqrnshfeyqntkhhwlpyehpdpkkr
chlycqsketgdvaymkqlvhdgthcsykdpysicvrgecvkvgcdkeigsnkvedkcgvcggdnshcrtvkgtftrtpr
klgylkmfdippgarhvliqedeasphilaiknqatghyilngkgeeaksrtfidlgvewdynieddieslhtdgplhdp
vivliipqendtrssltykyiihedsvptinsnnviqeeldtfewalkswsqvskpcgggfqytkygcrrksdnkmvhrs
fceankkpkpirrmcniqecthplwvaeewehctktcgssgyqlrtvrclqplldgtnrsvhskycmgdrpesrrpcnrv
pcpaqwktgpwsecsvtcgegtevrqvlcragdhcdgekpesvracqlppcndepclgdksifcqmevlarycsipgynk
lccescskrsstlpppylleaaethddvisnpsdlprslvmptslvpyhsetpakkmslssissvggpnayaafrpnskp
dganlrqrsaqqagsktvrlvtvpssppt krvhlssasqmaaasffaasdsigassqartskkdgkiidnrrptrsstle
r (1,201)
```

Fig. 8

GGAATTCGCGGCCGCGTCGACGTCAATACCAACTCCGAGCACACGGCCGTCATCAGCCTCTGCTCAGGAATGCTGGGCAC
ATTCCGGTCTCATGATGGGGATTATTTTATTGAACCACTACAGTCTATGGATGAACAAGAAGATGAAGAGGAACAAAACA
AACCCCACATCATTTATAGGCGCAGCGCCCCCCAGAGAGAGCCCTCAACAGGAAGGCATGCATGTGACACCTCAGAACAC
AAAAATAGGCACAGTAAAGACAAGAAGAAAACCAGAGCAAGAAAATGGGGAGAAAGGATTAACCTGGCTGGTGACGTAGC
AGCATTAAACAGCGGCTTAGCAACAGAGGCATTTTCTGCTTATGGTAATAAGACGGACAACACAAGAGAAAAGAGGACCC
ACAGAAGGACAAAACGTTTTTTATCCTATCCACGGTTTGTAGAAGTCTTGGTGGTGGCAGACAACAGAATGGTTTCATAC
CATGGAGAAAACCTTCAACACTATATTTTAACTTTAATGTCAATTGATGGGCCTTCCATATCTTTTAATGCTCAGACAAC
ATTAAAAAACCTTTGCCAGTGGCAGCATTCGAAGAACAGTCCAGGTGGAATCCATCATGATACTGCTGTTCTCTTAACAA
GACAGGATATCTGCAGAGCTCACGACAAATGTGATACCTTAGGCCTGGCTGAACTGGGAACCATTTGTGATCCCTATAGA
AGCTGTTCTATTAGTGAAGATAGTGGATTGAGTACAGCTTTTACGATCGCCCATGAGCTGGGCCATGTGTTTAACATGCC
TCATGATGACAACAACAAATGTAAAGAAGAAGGAGTTAAGAGTCCCCAGCATGTCATGGCTCCAACACTGAACTTCTACA
CCAACCCCTGGATGTGGTCAAAGTGTAGTCGAAAATATATCACTGAGTTTTTAGACACTGGTTATGGCGAGTGTTTGCTT
AACGAACCTGAATCCAGACCCTACCCTTTGCCTGTCCAACTGCCAGGCATCCTTTACAACGTGAATAAACAATGTGAATT
GATTTTTGGACCAGGTTCTCAGGTGTGCCCATATATGATGCAGTGCAGACGGCTCTGGTGCAATAACGTCAATGGAGTAC
ACAAAGGCTGCCGGACTCAGCACACACCCTGGGCCGATGGGACGGAGTGCGAGCCTGGAAAGCACTGCAAGTATGGATTT
TGTGTTCCCAAAGAAATGGATGTCCCCGTGACAGATGGATCCTGGGGAAGTTGGAGTCCCTTTGGAACCTGCTCCAGAAC
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GTAGAATGAAATTTAAGTCCTGCAACACGGAGCCATGTCTCAAGCAGAAGCGAGACTTCCGAGATGAACAGTGTGCTCAC
TTTGACGGGAAGCATTTTAACATCAACGGTCTGCTTCCCAATGTGCGCTGGGTCCCTAAATACAGTGGAATTCTGATGAA
GGACCGGTGCAAGTTGTTCTGCAGAGTGGCAGGGAACACAGCCTACTATCAGCTTCGAGACAGAGTGATAGATGGAACTC
CTTGTGGCCAGGACACAAATGATATCTGTGTCCAGGGCCTTTGCCGGCAAGCTGGATGCGATCATGTTTTAAACTCAAAA
GCCCGGAGAGATAAATGTGGGGTTTGTGGTGGCGATAATTCTTCATGCAAAACAGTGGCAGGAACATTTAATACAGTACA
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CAGACGATGACAACTACTTAGCTTTATCAAGCAGTAAAGGTGAATTCTTGCTAAATGGAAACTTTGTTGTCACAATGGCC
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TCGCATTGAGCAAGAACTTTTGCTTCAGGTTTTGTCGGTGGGAAAGTTGTACAACCCCGATGTACGCTATTCTTTCAATA
TTCCAATTGAAGATAAACCTCAGCAGTTTTACTGGAACAGTCATGGGCCATGGCAAGCATGCAGTAAACCCTGCCAAGGG
GAACGGAAACGAAAACTTGTTTGCACCAGGGAATCTGATCAGCTTACTGTTTCTGATCAAAGATGCGATCGGCTGCCCCA
GCCTGGACACATTACTGAACCCTGTGGTACAGACTGTGACCTGAGGTGGCATGTTGCCAGCAGGAGTGAATGTAGTGCCC

Fig. 9A

AGTGTGGCTTGGGTTACCGCACATTGGACATCTACTGTGCCAAATATAGCAGGCTGGATGGGAAGACTGAGAAGGTTGAT
GATGGTTTTTGCAGCAGCCATCCCAAACCAAGCAACCGTGAAAAATGCTCAGGGGAATGTAACACGGGTGGCTGGCGCTA
TTCTGCCTGGACTGAATGTTCAAAAAGCTGTGACGGTGGGACCCAGAGGAGAAGGGCTATTTGTGTCAATACCCGAAATG
ATGTACTGGATGACAGCAAATGCACACATCAAGAGAAAGTTACCATTCAGAGGTGCAGTGAGTTCCCTTGTCCACAGTGG
AAATCTGGAGACTGGTCAGAGTGCTTGGTCACCTGTGGAAAAGGGCATAAGCACCGCCAGGTCTGGTGTCAGTTTGGTGA
AGATCGATTAAATGATAGAATGTGTGACCCAGAGGTCGACGCGGCCGCGAATTCCGCCGATACTGACGGGCTCCAGGAGT
CGTCGCCACCAATCCCCATATGGAAACCGTCGATATTCAGCCATGTGCCTTCAAGCCGAATTCCAG

Fig. 9B

GIRGRVDVNTNSEHTAVISLCSGMLGTFRSHDGDYFIEPLQSMDEQEDEEEQNKPHIIYRRSAPQREPSTGRHACDTSEH
KNRHSKDKKKTRARKWGERINLAGDVAALNSGLATEAFSAYGNKTDNTREKRTHRRTKRFLSYPRFVEVLVVADNRMVSY
HGENLQHYILTLMSIDGPSISFNAQTTLKNLCQWQHSKNSPGGIHHDTAVLLTRQDICRAHDKCDTLGLAELGTICDPYR
SCSISEDSGLSTAFTIAHELGHVFNMPHDDNNKCKEEGVKSPQHVMAPTLNFYTNPWMWSKCSRKYITEFLDTGYGECLL
NEPESRPYPLPVQLPGILYNVNKQCELIFGPGSQVCPYMMQCRRLWCNNVNGVHKGCRTQHTPWADGTECEPGKHCKYGF
CVPKEMDVPVTDGSWGSWSPFGTCSRTCGGGIKTAIRECNRPEPKNGGKYCVGRRMKFKSCNTEPCLKQKRDFRDEQCAH
FDGKHFNINGLLPNVRWVPKYSGILMKDRCKLFCRVAGNTAYYQLRDRVIDGTPCGQDTNDICVQGLCRQAGCDHVLNSK
ARRDKCGVCGGDNSSCKTVAGTFNTVHYGYNTVVRIPAGATNIDVRQHSFSGETDDDNYLALSSSKGEFLLNGNFVVTMA
KREIRIGNAVVEYSGSETAVERINSTDRIEQELLLQVLSVGKLYNPDVRYSFNIPIEDKPQQFYWNSHGPWQACSKPCQG
ERKRKLVCTRESDQLTVSDQRCDRLPQPGHITEPCGTDCDLRWHVASRSECSAQCGLGYRTLDIYCAKYSRLDGKTEKVD
DGFCSSHPKPSNREKCSGECNTGGWRYSAWTECSKSCDGGTQRRRAICVNTRNDVLDDSKCTHQEKVTIQRCSEFPCPQW
KSGDWSECLVTCGKGHKHRQVWCQFGEDRLNDRMCDPEVDAAANSADTDGLQESSPPIPIWKPSIFSHVPSSRIP

Fig. 10

cacatatgcacgagagagacagaggaggaaagagacagagacaaaggcacagcggaagaaggcagagacagggcaggcac
agaagcggcccagacagagtcctacagagggagaggccagagaagctgcagaagacacaggcagggagagacaaagatcc
aggaaaggagggctcaggaggagagtttggagaagccagacccctgggcacctctcccaagcccaaggactaagttttct
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gaggagctttccaaagctagggtgtggaggacttggtgccctagacggcctcagtccctcccagctgcagtaccagtgcc
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gagatccggagtcggtggcatctctgcactgggatgggggagccctgttaggcgtgttacaatatcggggggctgaactc
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tgctgcctacaaccaccgcaccgacctcttcaagagcttcccagggcccatggactgggttcctcgctacacaggcgtgg
ccccccaggaccagtgcaaactcacctgccaggcccgggcactgggctactactatgtgctggagccacgggtggtagat

Fig. 11A

gggacccccctgttccccggacagctcctcggtctgtgtccagggccgatgcatccatgctggctgtgatcgcatcattgg
ctccaagaagaagtttgacaagtgcatggtgtgcggaggggacggttctggttgcagcaagcagtcaggctccttcagga
aattcaggtacggatacaacaatgtggtcactatccccgcgggggccacccacattcttgtccggcagcagggaaaccct
ggccaccggagcatctacttggccctgaagctgccagatggctcctatgccctcaatggtgaatacacgctgatgccctc
cccacagatgtggtactgcctggggcagtcagcttgcgctacagcggggccactgcagcctcagagacactgtcaggcc
atgggccactggcccagcctttgacactgcaagtcctagtggctggcaacccccaggacacacgcctccgatacagcttc
ttcgtgccccggccgacccccttcaacgccacgccccactccccaggactggctgcaccgaagagcacagattctggagat
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gggctgacagacagccctccatctaaactgccccctctgccctgcgggtcacaggagggagggggaaggcagggagggcc
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gcatcctccgcctcccgggttcaagtgattctcatgcctcagcctcctgagtagctgggattacaggctcctgccaccac
gcccagctaattttgttttgttttgtttggagacagagtctcgctattgtcaccagggctggaatgatttcagctcact
gcaaccttcgccacctgggttccagcaattctcctgcctcagcctcccgagtagctgagattataggcacctaccaccac
gcccggctaattttgtatttttagtagagacggggtttcaccatgttggccaggctggtctcgaactcctgaccttagg
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ggcctcccaaagtgctgggattacaggtgtgagccaccacgcccggtacatattttttaaattgaattctactatttatg
tgatccttttggagtcagacagatgtggttgcatcctaactccatgtctctgagcattagatttctcatttgccaataat
aatacctcccttagaagtttgttgtgaggattaaataatgtaaataaagaactagcataac

Fig. 11B

MSQTGSHPGRGLAGRWLWGAQPCLLLPIVPLSWLVWLLLLLLASLLPSARLASPLPREEEIVFPEKLNGSVLPGSGTPAR
LLCRLQAFGETLLLELEQDSGVQVEGLTVQYLGQAPELLGGAEPGTYLTGTINGDPESVASLHWDGGALLGVLQYRGAEL
HLQPLEGGTPNSAGGPGAHILRRKSPASGQGPMCNVKAPLGSPSPRPRRAKRFASLSRFVETLVVADDKMAAFHGAGLKR
YLLTVMAAAAKAFKHPSIRNPVSLVVTRLVILGSGEEGPQVGPSAAQTLRSFCAWQRGLNTPEDSDPDHFDTAILFTRQD
LCGVSTCDTLGMADVGTVCDPARSCAIVEDDGLQSAFTAAHELGHVFNMLHDNSKPCISLNGPLSTSRHVMAPVMAHVDP
EEPWSPCSARFITDFLDNGYGHCLLDKPEAPLHLPVTFPGKDYDADRQCQLTFGPDSRHCPQLPPPCAALWCSGHLNGHA
MCQTKHSPWADGTPCGPAQACMGGRCLHMDQLQDFNIPQAGGWGPWGPWGDCSRTCGGGVQFSSRDCTRPVPRNGGKYCE
GRRTRFRSCNTEDCPTGSALTFREEQCAAYNHRTDLFKSFPGPMDWVPRYTGVAPQDQCKLTCQARALGYYYVLEPRVVD
GTPCSPDSSSVCVQGRCIHAGCDRIIGSKKKFDKCMVCGGDGSGCSKQSGSFRKFRYGYNNVVTIPAGATHILVRQQGNP
GHRSIYLALKLPDGSYALNGEYTLMPSPTDVVLPGAVSLRYSGATAASETLSGHGPLAQPLTLQVLVAGNPQDTRLRYSF
FVPRPTPSTPRPTPQDWLHRRAQILEILRRRPWAGRK

Fig. 12

Rat ADAMTS 5 DNA

```
ACTCACTATA GGGCTCGAGC GGCCGCCCGG GCAGGTCAGA GGCTCACTGG CAGCTCTCTA      60
GACCTGCGAC GCTGCTTCTA TTCCGGGTAT GTGAACGCGG AGCCAGACTC CTTTGCTGCT     120
GTAAGCCTAT GCGGGGGTCT CCGCGGAGCC TTTGGCTACC AAGGTGCGGA GTATGTCATT     180
AGCCCTCTGC CCAACACCAG CGCGCCTGAG GCGCAGCGTC ATAGCCAGGG CGCACACCTT     240
CTCCAGCGCC GGGGTGCTCC CGTAGGGCCT TCCGGAGACC CTACCTCTCG CTGCGGGGTG     300
GCCTCGGGCT GGAACCCCGC CATCCTGAGG GCCTTGGACC CTTATAAACC ACGGCGGACG     360
GGCGTGGGCG AAAGCCACAA CCGGCGCAGG TCTGGGCGCG CCAAGCGCTT CGTGTCTATA     420
CCACGGTACG TGGAGACACT GGTGGTGGCG GACGAGTCAA TGGTCAAGTT TCACGGCGCG     480
GATTTGGAAC ATTATCTGCT GACGCTGCTG GCCACGGCGG CGCGACTCTA CCGCCACCCC     540
AGCATCCTCA ACCCTATCAA CATCGTTGTG GTCAAGGTGT TACTCTTAGG AGATCGTGAC     600
ACTGGGCCCA AGGTCACAGG CAACGCGGCC CTGACTCTGC GCAACTTCTG TGCCTGGCAG     660
AAAAAGTTGA ACAAAGTGAG CGACAAGCAC CCCGAGTACT GGGACACAGC CATCCTCTTC     720
ACCAGACAGG ACCTATGCGG GGCTACCACC TGTGACACCT TGGGCATGGC TGATGTGGGC     780
ACCATGTGTG ATCCCAAGAG AAGCTGCTCT GTCATCGAGG ACGATGGGCT TCCGTCGGCC     840
TTCACCACTG CCCATGAGCT GGGCCATGTG TTCAACATGC CCCATGACAA CGTGAAGGTG     900
TGTGAGGAGG TGTTTGGGAA GCTCAGAGCC AACCACATGA TGTCTCCGAC ACTCATCCAG     960
ATCGACCGTG CCAACCCCTG GTCAGCCTGC AGTGCTGCCA TTATCACCGA CTTCCTGGAC    1020
AGCGGGCACG GTGACTGCCT CCTGGACCAG CCCAGCAAGC CCATCACCCT GCCTGAGGAC    1080
CTGCCAGGCA CAAGCTACAG TTTGAGCCAA CAGTGCGAGC TGGCCTTTGG GGTGGGCTCT    1140
AAGCCCTGCC CATATATGCA GTACTGTACA AAGCTGTGGT GCACCGGCAA GGCCAAGGGG    1200
CAGATGGTGT GCCAGACTCG CCACTTCCCC TGGGCAGATG GCACCAGCTG TGGTGAGGGC    1260
AAGTTCTGCC TCAAGGGAGC CTGCGTGGAG AGACACAACC CAAACAAGTA CCGGGTGGAC    1320
GGCCCTTGGG CCAAGTGGGA GCCTTATGGT CCCTGCTCGC GCACCTGCGG TGGGGGCGCG    1380
CAGCTGGCCC GGAGGCAAGT GCAAGCAACC CTACCCCTGC CAACGGGCGG GAAGTACTGC    1440
GAGGGAGTGA GAGTGAAATA CCGATCTTGC AACTTGGAGC CCTGCCCCAG CTCAGCCTCT    1500
GGCAAGAGCT TCCGGGAA                                                  1518
```

Fig. 13

THYRARAAARAGQRLTGSSLDLRRCFYSGYVNAEPDSFAAVSLCGGLRGAFGYQGAEYVISPLPNTSAPEAQRHSQGAHL
LQRRGAPVGPSGDPTSRCGVASGWNPAILRALDPYKPRRTGVGESHNRRRSGRAKRFVSIPRYVETLVVADESMVKFHGA
DLEHYLLTLLATAARLYRHPSILNPINIVVVKVLLLGDRDTGPKVTGNAALTLRNFCAWQKKLNKVSDKHPEYWDTAILF
TRQDLCGATTCDTLGMADVGTMCDPKRSCSVIEDDGLPSAFTTAHELGHVFNMPHDNVKVCEEVFGKLRANHMMSPTLIQ
IDRANPWSACSAAIITDFLDSGHGDCLLDQPSKPITLPEDLPGTSYSLSQQCELAFGVGSKPCPYMQYCTKLWCTGKAKG
QMVCQTRHFPWADGTSCGEGKFCLKGACVERHNPNKYRVDGPWAKWEPYGPCSRTCGGGAQLARRQVQATLPLPTGGKYC
EGVRVKYRSCNLEPCPSSASGKSFR

Fig. 14

GATGCATCTAAGCCCTGGTCCAAATGCACTTCAGCCACCATCACAGAATTCCTGGATGATGGCCATGGTAACTGTTTGCT
GGACCTACCACGAAAGCAGATCCTGGGCCCCGAAGAACTCCCAGGACAGACCTACGATGCCACCCAGCAGTGCAACCTTA
CATTCGGGCCTGAGTACTCCGTGTGTCCCGGCATGGATGTCTGTGCTCCCCTGTGGTGTGCTGTGGTACGCCAGGGCCAG
ATGGTCTGTCTGACCAAGAAGCTTCCTGCGGTGGAAGGGACGCCTTGTGGAAAGGGGAGAATCTGCCTGCAGGGCAAATG
TGTGGACAAAACCAAGAAAAAATATTATTCAACGTCAAGCCATGGCAACTGGGGATCTTGGGGATCCTGGGGCCAGTGTT
CTCGCTCATGTGGAGGAGGAGTGCAGTTTGCCTATCGTCGCTGTAATAACCCTGCTCCCAGAAACAACGGACGCTACTGC
ACAGGGAAGAGGGCCATCTACCGCTCCTGCAGTCTCATGCCCTGCCCACCCAATGGTAAATCATTTCGTCATGAACAGTG
TGAGGCCAAAAATGGCTATCAGTCTGATGCAAAAGGAGTCAAAACTTTTGTGGAATGGGTTCCCAAATATGCAAGTGTCC
TGCCCAGCGATGTGTGCAAGCTGACCTGCAGAGCCAAAGGGACTGGCTACTATGTGGTATTTTCTCCAAAGGTGACCGAT
GGCACTGAATGTAGGCCGTACAGTAATTCCGTCTGCGTCCGGGGGAAGTGTGTGAGAACTGGCTGTGACGGCATCATTGG
CTCAAAGCTGCAGTATGACAAGTGCGGAGTATGTGGAGGAGACAACTCCAGCTGTACAAAGATTGTTGGAACCTTTAATA
AGAAAAGTAAGGGTTCANCTGACGTGGTGAGGATTCCTGAAGGGGCAACCCACATAAAAGTTCGACAGTTCAAAGCCAAA
GACCAGACTAGATTCACTGCCTATTTAGCCCTGAAAAAGAAAAACGGTGAGTACCTTATCAATGGAAAGTACATGATCTC
CACTTCAGAGACTATCATTGACATCAATGGAACAGTCATGAACTATAGCGGTTGGAGCCACAGGGATGACTTCCTGCATG
GCATGGGCTACTCTGCCACGAAGGAAATTCTAATAGTGCAGATTCTTGCAACAGACCCCACTAAACCATTAGATGTCCGT
TATAGCTTTTTTGTTCCCAAGAAGTCCACTCCAAAAGTAAACTCTGTCACTAGTCATGGCAGCAATAAAGTGGGATCACA
CACTTCGCAGCCGCAGTGGGTCACGGGCCCATGGCTCGCCTGCTCTAGGACCTGTGACACAGGTTGGCACACCAGAACGG
TGCAGTGCCAGGATGGAAACCGGAAGTTAGCAAAAGGATGTCCTCTCTCCCAAAGGCCTTCTGCGTTTAAGCAATGCTTG
TTGAAGAAATGTTAG

Fig. 15

DASKPWSKCTSATITEFLDDGHGNCLLDLPRKQILGPEELPGQTYDATQQCNLTFGPEYSVCPGMDVCAPLWCAVVRQGQ
MVCLTKKLPAVEGTPCGKGRICLQGKCVDKTKKKYYSTSSHGNWGSWGSWGQCSRSCGGGVQFAYRRCNNPAPRNNGRYC
TGKRAIYRSCSLMPCPPNGKSFRHEQCEAKNGYQSDAKGVKTFVEWVPKYASVLPSDVCKLTCRAKGTGYYVVFSPKVTD
GTECRPYSNSVCVRGKCVRTGCDGIIGSKLQYDKCGVCGGDNSSCTKIVGTFNKKSKGSXDVVRIPEGATHIKVRQFKAK
DQTRFTAYLALKKKNGEYLINGKYMISTSETIIDINGTVMNYSGWSHRDDFLHGMGYSATKEILIVQILATDPTKPLDVR
YSFFVPKKSTPKVNSVTSHGSNKVGSHTSQPQWVTGPWLACSRTCDTGWHTRTVQCQDGNRKLAKGCPLSQRPSAFKQCL
LKKC

Fig. 16

```
    M---------------------------------------  Majority
             10        20        30        40

1   M----------GDVQ-RAARS----------RGSLSAHML  mADAMTS-1
1   ----------------------------------------  hADAMTS-2
1   --GIR-----------------------------------  hADAMTS-3
1   LLGARQYRRNSGPPTPAPETSIANSKHPARLSRAAPPGAQ  rADAMTS-4
1   M----------SQTGSHPGRGLAGR----WLWGAQPCLLL  KIAA0688
1   SL--------------------------------------  KIAA0366
1   MDGRWQCS--------------------------------  KIAA0605

    -------------LLLLAL-TVLLSAD--AG-P---EEEL  Majority
             50        60        70        80

20  -------------LLLLASITMLLCARGAHGRPTEEDEEL  mADAMTS-1
1   ----------------------------------------  hADAMTS-2
4   ----------------------------------------  hADAMTS-3
41  RTMRLEWASLLLLLLLLCASCLALAADNPAAAPAQDKTRQ  rADAMTS-4
27  PIVPLSW---LVWLLLLLLASLLPSAR--LASPLPREEEI  KIAA0688
3   ------------WLIAAALVEVRTSADGQAGNEEMVQIDL  KIAA0366
9   -----CWAWFLLVLAVVAGDTVSTGSTDNSPTSNSLEGGT  KIAA0605

    V----P----------------LRG---P-G--GTTSRL-  Majority
             90       100       110       120

47  VL---PS--------------LERA---P-GHDSTTTRL-  mADAMTS-1
1   ----------------------------------------  hADAMTS-2
4   ----------------------------------------  hADAMTS-3
81  PR---AAAAAAQPDQRQWEETQERGHLQPLARQRRSSGLV  rADAMTS-4
62  VF---PE--------------KLNGSVLP-G-SGTPARLL  KIAA0688
31  PIKRYREYELVTPVSTNLEGRYLSHTLSASHKKRSARDVS  KIAA0366
44  DATAFW-----------WGEWTKWTAFSRSCGGGVTSQER  KIAA0605

    -NLD----------------G----L-LERDSGV-APG--  Majority
            130       140       150       160

65  -RLDAF--------------GQQLHLKLQPDSGFLAPGFT  mADAMTS-1
1   ----------------------------------------  hADAMTS-2
4   ----------GRVD--------------------------  hADAMTS-3
118 QNIDQLYSGGGKVGYLVYAGGRRFLLDLERDDTVGAAGGI  rADAMTS-4
83  CRLQAF--------------GETLLLELEQDSGVQVEGLT  KIAA0688
71  SNPEQLF-------FNITAFGKDFHLRLKPNTQLVAPGAV  KIAA0366
73  HCLQ------------------------QRRKSVPGPG--  KIAA0605
```

Fig. 17A

```
    VQ---TGLSP-------------GA------------HCP  Majority
              170       180       190       200

90  LQ--TVGRSPGSEAQHLD---PTGD----------LAHCF  mADAMTS-1
1   ----------------------------------------  hADAMTS-2
8   ----------------------------------------  hADAMTS-3
158 VT--AGGLSASS-----------GH----------RGHCF  rADAMTS-4
109 VQ--YLGQAP----ELLG-----GA----------EPGTY  KIAA0688
104 VEWHETSLVPGNITDPINNHQPGSATYRIRKTEPLQTNCA  KIAA0366
87  -NRTCTGTSKRYQLCRVQECPPDGRSFREEQCVSFNSHVY  KIAA0605

    Y-GTVNGDPGSXAALSLCGG-LLGXF--XVDGAEYFIEPL  Majority
              210       220       230       240

115 YSGTVNGDPGSAAALSLCEG-VRGAF--YLQGEEFFIQPA  mADAMTS-1
1   ----------------------------------------  hADAMTS-2
8   ----VNTNSEHTAVISLCSG-MLGTF--RSHDGDYFIEPL  hADAMTS-3
175 YRGTVDGSPRSLAVFDLCGG-LDGFF--AVKHARYTLRPL  rADAMTS-4
128 LTGTINGDPESVASLHWDGGALLGVL--QYRGAELHLQP-  KIAA0688
144 YVGDIVDIPGTSVAISNCDG-LAGMI--KSDNEEYFIEPL  KIAA0366
126 NGRTHQWKPLYPDDYVHISSKPCDLHCTTVDGQRQLMVPA  KIAA0605

    -------LE-GRPXEEGG-RP---Y-R-----H-LRRR-P  Majority
              250       260       270       280

152 PGVATERLAPAVPEEESSARP---------QFHILRRRRR  mADAMTS-1
1   ----------------------------------------  hADAMTS-2
41  QSMD------EQEDEEEQNKPHIIYRRSA------PQREP  hADAMTS-3
212 --LRGSWAESERVYGDGSSRILHVYTREGFSFEALPPRTS  rADAMTS-4
165 -------LEGGTPNSAGG--P---------GAHILRRKSP  KIAA0688
181 --------ERGKQMEEEKGRIHVVYKRSA-----------  KIAA0366
166 RDGTSCKLTDLRGVCVSGKCEPIGCDGVLFSTHTLDKCGI  KIAA0605

    CSG-GA-CGVVE--PLHSSS-RPT----------------  Majority
              290       300       310       320

183 GSG-GAKCGVMDDETLPTSDSRPESQNTRNQW--------  mADAMTS-1
1   ----------------------------------------  hADAMTS-2
69  STGRHA-CDTSEHKNRHSKDKKKTRARKWGERINLAGDVA  hADAMTS-3
250 CETPASPSGAQESPSVHSSSRRRTELAPQ-----------  rADAMTS-4
187 ASGQGPMCNVKA--PLGSPSPRPR----------------  KIAA0688
202 ----------VEQAPIDMSKDFHYRESDLEGLDDLGTVYG  KIAA0366
206 CQGDGSSCTHVT---------------------------G  KIAA0605
```

Fig. 17B

```
    - - - - G L A H T - - S - - - - - - - - - - - - - - - R R T K R F A S E A R F -   Majority
                      330                 340                 350                 360
214 - - - P V R D P T P Q D A G K P S G P G S - - - - - - I R K K R F V S S P R Y -   mADAMTS-1
1   - - - - - - - - - - - - - - - - - - - - - - - - - - - - R T K R F V S E A R F -   hADAMTS-2
108 A L N S G L A T E A F S A Y G N K T D N T R E K R T H R R T K R F L S Y P R F -   hADAMTS-3
279 - - - - L L D H S A F S P A G N A G P Q T W - - - - W R R R R R S I S R A R Q -   rADAMTS-4
209 - - - - - - - - - - - - - - - - - - - - - - - - - - - - R A K R F A S L S R F -   KIAA0688
232 N I H Q Q L N E T - - - - - - - - - - - - - - - - - - M R R R R H A G E N D Y N   KIAA0366
219 N Y R K G N A H L G Y S L V T H I P A G A R D I Q I V E R K K - - - - - - - - S   KIAA0605

    V E V L L V A D D S M A A F H G A G - L Q N Y L L T L M S I A A R I Y K H P S I   Majority
                      370                 380                 390                 400
244 V E T M L V A D Q S M A D F H G S G - L K H Y L L T L F S V A A R F Y K H P S I   mADAMTS-1
12  V E T L L V A D A S M A A F Y G A D - L Q N H I L T L M S V A A R I Y K H P S I   hADAMTS-2
147 V E V L V V A D N R M V S Y H G E N - L Q H Y I L T L M S I D - - - - - - - - -   hADAMTS-3
310 V E L L L V A D S S M A K M Y G R G - L Q H Y L L T L A S I A N R L Y S H A S I   rADAMTS-4
220 V E T L V V A D D K M A A F H G A G - L K R Y L L T V M A A A A K A F K H P S I   KIAA0688
254 I E V L L G V D D S V V R F H G K E H V Q N Y L L T L M N I V N E I Y H D E S L   KIAA0366
251 A D V L A L A D E A G Y Y F F N G - - - - N Y K V D - - - - S P K N F N I A G T   KIAA0605

    R N S I S L V V V K V V V L G D E K K G P E V S X - N A A L T L R N F C N W Q H   Majority
                      410                 420                 430                 440
283 R N S I S L V V V K I L V I Y E E Q K G P E V T S - N A A L T L R N F C N W Q K   mADAMTS-1
51  K N S I N L M V V K V L I V E D E K W G P E V S D - N G G L T L R N F C N W Q R   hADAMTS-2
177 - - - - - - - - - - - - - - - - - - - G P S I S F - N A Q T T L K N L C Q W Q H   hADAMTS-3
349 E N H I R L A V V K V V V L T D - - K S L E V S K - N A A T T L K N F C K W Q H   rADAMTS-4
259 R N P V S L V V T R L V I L G S G E E G P Q V G P - S A A Q T L R S F C A W Q R   KIAA0688
294 G V H I N V V L V R M I M L G Y A K S I S L I E R G N P S R S L E N V C R W A S   KIAA0366
283 V V K Y R - - - - R P M D V Y E T G I E Y I V A Q G P T N Q G L N V M - V W N Q   KIAA0605

    Q H N S P S D R H P E H Y D T A I L L T R Q D L C G S H G - C D T L G M A D V G   Majority
                      450                 460                 470                 480
322 Q H N S P S D R D P E H Y D T A I L F T R Q D L C G S H T - C D T L G M A D V G   mADAMTS-1
90  R F N Q P S D R H P E H Y D T A I L L T R Q N F C G Q E G L C D T L G V A D I G   hADAMTS-2
197 S K N S P G G I - - - H H D T A V L L T R Q D I C R A H D K C D T L G L A E L G   hADAMTS-3
386 Q H N Q L G D D H E E H Y D A A I L F T R E D L C G H H S - C D T L G M A D V G   rADAMTS-4
298 G L N T P E D S D P D H F D T A I L F T R Q D L C G V S T - C D T L G M A D V G   KIAA0688
334 Q Q Q R S D L N H S E H H D H A I F L T R Q D F - G P A G M - - - Q G Y A P V T   KIAA0366
318 N G K S P S I T - - - - F E Y T L L Q P P H E - - - S R P Q P I Y Y G F S E S A   KIAA0605
```

Fig. 17C

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    T I C D P X R S C S V I E D D G L Q A A F T V A H E L G H V L N M P H D - D S K   Majority
                        490                 500                 510                 520
361 T V C D P S R S C S V I E D D G L Q A A F T T A H E L G H V F N M P H D - D A K   mADAMTS-1
130 T I C D P N K S C S V I E D E G L Q A A H T L A H E L G H V L S M P H D - D S K   hADAMTS-2
234 T I C D P Y R S C S I S E D S G L S T A F T I A H E L G H V F N M P H D - D N N   hADAMTS-3
425 T I C S P E R S C A V I E D D G L H A A F T V A H E I G H L L G L S H D - D S K   rADAMTS-4
337 T V C D P A R S C A I V E D D G L Q S A F T A A H E L G H V F N M L H D - N S K   KIAA0688
370 G M C H P V R S C T L N H E D G F S S A F V V A H E T G H V L G M E H D G Q G N   KIAA0366
351 - - - - - - - - - - - - - E S Q G L D G A - - - - - - - G L M G F I P H N G - - -   KIAA0605

    P C - S L N G P X G S S R H V M - A P L L X H L D H S X P W S P C S A Q E I T E   Majority
                        530                 540                 550                 560
400 H C A S L N G V T G D S - H L M - A S M L S S L D H S Q P W S P C S A Y M V T S   mADAMTS-1
169 P C T R L F G P M G K H - H V M - A P L F V H L N Q T L P W S P C S A M Y L T E   hADAMTS-2
273 K C K E - - E G V K S P Q H V M - A P T L N F Y T N P W M W S K C S R K Y I T E   hADAMTS-3
464 F C E E N F G S - T E D K R L M - S S I L T S I D A S K P W S K C T S A T I T E   rADAMTS-4
376 P C I S L N G P L S T S R H V M - A P V M A H V D P E E P W S P C S A R F I T D   KIAA0688
410 R C - - - - G D E T A M G S V M - A P L V Q A A F H R Y H W S R C S G Q E L K R   KIAA0366
369 - - - S L Y G Q A S S E R L G L D N R L F G H P G L D M E L G P S Q G Q E T N E   KIAA0605

    F - L D N G H G D C L L D K P E A - P L P L P V E L P G - - I L Y D A D E Q C Q   Majority
                        570                 580                 590                 600
438 F - L D N G H G E C L M D K P Q N - P I K L P S D L P G - - T L Y D A N R Q C Q   mADAMTS-1
207 L - L D G G H G D C L L D A P A A - A L P L P T G L P G R M A L Y Q L D Q Q C R   hADAMTS-2
310 F - L D T G Y G E C L L N E P E S R P Y P L P V Q L P G - - I L Y N V N K Q C E   hADAMTS-3
502 F - L D D G H G N C L L D V P R K - Q I L G P E E L P G Q T - - Y D A T Q Q C N   rADAMTS-4
415 F - L D N G Y G H C L L D K P E A - P L H L P V T F P G K D - - Y D A D R Q C Q   KIAA0688
445 Y - I H S Y - - D C L L D D P F D H D W P K L P E L P G - - I N Y S M D E Q C R   KIAA0366
406 V C E Q A G G G A C - E G P P R G K G F R D R N V T G T P L T G D K D D E E V D   KIAA0605

    L T F G P G S K H C P X F S A - D V C A Q L W C A G V D - G G H X V C Q T K H G   Majority
                        610                 620                 630                 640
474 F T F G E E S K H C P D A A S - - T C T T L W C T G T S - G G L L V C Q T K H -   mADAMTS-1
245 Q I F G P D F R H C P N T S A Q D V C A Q L W C H - T D - G A E P L C H T K N G   hADAMTS-2
347 L I F G P G S Q V C P Y M M Q - - - C R R L W C N N V N - G V H K G C R T Q H T   hADAMTS-3
538 L T F G P E Y S V C P G M - - - D V C A R L W A A V V R - Q G Q M V C L T K K -   rADAMTS-4
451 L T F G P D S R H C P Q L P P P - - C A A L W C S G H L - N G H A M C Q T K H S   KIAA0688
480 F D F G V G Y K M C T A F R T F D P C K Q L W C S H P D - N P Y - F C K T K K G   KIAA0366
445 T H F A S Q - - - - E F F S A N A I S D Q L L G A G S D L K D F T L N E T V N S   KIAA0605
```

Fig. 17D

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    - - P W A D G T P C G P G K X - C K A G S - C V P K E E N E R - - P V V D G G W   Majority
                      650                 660                 670                 680
510 - F P W A D G T S C G E G K W - C V S G K - C V N K T D M K H F A T P V H G S W   mADAMTS-1
283 S L P W A D G T P C G P G H L - C S E G S - C L P E E E V E R P K P V V D G G W   hADAMTS-2
383 - - P W A D G T E C E P G K H - C K Y G - F C V P K - E M D - - V P V T D G S W   hADAMTS-3
573 - L P A V R A L P V G K E E S A C K A N V W T K L R K N I T R H Q A M E I G G P   rADAMTS-4
488 - - P W A D G T P C G P A Q A - C M G G R - C L H M D Q L Q D F N I P Q A G G W   KIAA0688
518 - - P P L D G T E C A A G K W - C Y K G H - C M W K N A N Q Q - - - K Q D G N W   KIAA0366
481 I F A - - Q G A P - - - - - R S S L A E S F F V D Y E E N E - - - - - - - - - -   KIAA0605

    G P W G P W G D C S R T C G G S V Q F S L R E C N N P V P K N G G K Y C E G R -   Majority
                      690                 700                 710                 720
547 G P W G P W G D C S R T C G G G V Q Y T M R E C D N P V P K N G G K Y C E G K -   mADAMTS-1
321 A P W G P W G E C S R T C G G G V Q F S H R E C K D P E P Q N G G R Y C L G R -   hADAMTS-2
416 G S W S P F G T C S R T C G G G I K T A I R E C N R P E P K N G G K Y C V G R -   hADAMTS-3
612 G A P G V - - - - S V L A L A G E E Y S L P T A I A I T P H L E T V A A T A Q G   rADAMTS-4
524 G P W G P W G D C S R T C G G G V Q F S S R D C T R P V P R N G G K Y C E G R -   KIAA0688
551 G S W T K F G S C S R T C G T G V R F R T R Q C N N P M P I N G G Q D C P G - V   KIAA0366
504 - - - - - - - - - - - - - - G A G P Y L L N G S Y - - L E L S S D R V A N S S S   KIAA0605

    R A K Y Q S C N T E D C P K H X G K T F R A E Q C A K Y N - A F S Y X N K G X X   Majority
                      730                 740                 750                 760
586 R V R Y R S C N I E D C P D N N G K T F R E E Q C E A H N - E F S K A S F G N E   mADAMTS-1
360 R A K Y Q S C H T E E C P P D - G K S F R E Q Q C E K Y N - A Y N Y T D M D G N   hADAMTS-2
455 R M K F K S C N T E P C L K Q K - R D F R D E Q C A H F D G K H F N I N - G L L   hADAMTS-3
648 R G P Y - T V P A V S Y P A H L T A N L S A T S S V K P K M A I S P M Q K E S K   rADAMTS-4
563 R T R F R S C N T E D C P T G S A L T F R E E Q C A A Y N - H R T D L F K S F P   KIAA0688
590 N F E Y Q L C N T E E C Q K H F E - D F R A Q Q C Q Q R N S H F E Y Q N T K H -   KIAA0366
528 E A P F P N V S T S L L T S A G N R T H K A R T R P K A R K Q - - - - G V S P A   KIAA0605

    P X V E W V P K Y A G V S P K D R C K L T C R A K G T G Y Y Y V L E P K V V D G   Majority
                      770                 780                 790                 800
625 P T V E W T P K Y A G V S P K D R C K L T C E A K G I G Y F F V L Q P K V V D G   mADAMTS-1
398 - L L Q W V P K Y A G V S P R D R C K L F C R A R G R S E F K V F E A K V I D G   hADAMTS-2
493 P N V R W V P K Y S G I L M K D R C K L F C R V A G N T A Y Y Q L R D R V I D G   hADAMTS-3
687 T F V E W V P K Y A G V L P A D V C K L T C R A K G T G Y Y V V F S P K V T D G   rADAMTS-4
602 G P M D W V P R Y T G V A P Q D Q C K L T C Q A R A L G Y Y Y V L E P R V V D G   KIAA0688
628 - - - H W L P - Y E H P D P K K R C H L Y C Q S K E T G D V A Y M K Q L V H D G   KIAA0366
564 D M Y R W K - - - - - L S S H E P C S A T C T T G V M S A Y - - - - - - - - - -   KIAA0605
```

Fig. 17E

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                810       820       830       840
    TPCS-PDSNSVCVRGQCVKAGCDEIIGSKKKFDKCGVCGG  Majority
665 TPCS-PDSTSVCVQGQCVKAGCDRIIDSKKKFDKCGVCGG  mADAMTS-1
437 TLCG-PETLAICVRGQCVKAGCDHVVDSFWKLDKCGVCGG  hADAMTS-2
533 TPCG-QDTNDICVQGLCRQAGCDHVLNSKARRDKCGVCGG  hADAMTS-3
727 TECR-PYSNSVCVRGRCVRTGCDGIIGSKLQYDKCGVCGG  rADAMTS-4
642 TPCS-PDSSSVCVQGRCIHAGCDRIIGSKKKFDKCMVCGG  KIAA0688
664 THCSYKDPYSICVRGECVKVGCDKEIGSNKVEDKCGVCGG  KIAA0366
589 ----------AMCVR-------------------------  KIAA0605

                850       860       870       880
    DGSSCKKVSGTFTKT--RYGYNDVVTIPAGATNILVRQRS  Majority
704 NGSTCKKMSGIVTST--RPGYHDIVTIPAGATNIEVKHRN  mADAMTS-1
476 KGNSCRKGSGSLTPT--NYGYNDIVTIPAGATNIDVKQRS  hADAMTS-2
572 DNSSCKTVAGTFNTV--HYGYNTVVRIPAGATNIDVRQHS  hADAMTS-3
766 DNSSCTKIIGTFNKK--SKGYTDVVRIPEGATHIKVRQFK  rADAMTS-4
681 DGSGCSKQSGSFRKF--RYGYNNVVTIPAGATHILVRQQG  KIAA0688
704 DNSHCRTVKGTFTRTPRKLGYLKMFDIPPGARHVLIQEDE  KIAA0366
594 --------------------YDGV----------------  KIAA0605

                890       900       910       920
    ASGHTN--NYLALKX-ADGEYLLNGNFTLSTSETDIDLKG  Majority
742 QRGSRNNGSFLAIRA-ADGTYILNGNFTLSTLEQDLTYKG  mADAMTS-1
514 HPGVQNDGNYLALKT-ADGQYLLNGNLAISAIEQDILVKG  hADAMTS-2
610 FSGETDDDNYLALSS-SKGEFLLNGNFVVTMAKREIRIGN  hADAMTS-3
804 AKDQTRFTAYLALKK-KTGEYLINGKYMISTSETIIDING  rADAMTS-4
719 NPGHRS--IYLALKL-PDGSYALNGEYTLMPSPTDVVLPG  KIAA0688
744 ASPH-----ILAIKNQATGHYILNGKGEEAKSRTFIDL--  KIAA0366
598 ----------------------------------------  KIAA0605

                930       940       950       960
    TV-LRYSGSSAALERLHS----PLKEPLTVQVLAV-GXT-  Majority
781 TV-LRYSGSSAALERIRS--FSPLKEPLTIQVLMV-GHAL  mADAMTS-1
553 TI-LKYSGSIATLERLQS--FRPLPEPLTVQLLAVPGEVF  hADAMTS-2
649 AV-VEYSGSETAVERINSTD--RIEQELLLQVLSV-GKLY  hADAMTS-3
843 TV-MNYSGWSHRDDFLHGMGYSATKEILIVQILA-TDPTK  rADAMTS-4
756 AVSLRYSGATAASETLSG--HGPLAQPLTLQVL-VAGNPQ  KIAA0688
777 GVEWDYN-IEDDIESLHTDG--PLHDPVIVLIIPQENDT-  KIAA0366
598 EVDDSYCDALTRPEPVHE----------------------  KIAA0605
```

Fig. 17F

```
     RPDVRYSFFVP----------------------------- Majority
                       970       980       990      1000
817  RPKIKFTYFM------------------------------ mADAMTS-1
590  PPKVKYTFFVPND--------------------------- hADAMTS-2
685  NPDVRYSFNIPIEDKP------------QQFYWNSHGPWQ hADAMTS-3
881  ALDVRHSFFVP----------------------------- rADAMTS-4
793  DTRLRYSFFVP----------------------------- KIAA0688
813  RSSLTYKYIIHEDSVPTINSNNVIQEELDTFEW-ALKSWS KIAA0366
616  -------FCAGRECQPR---------------WET-SSWS KIAA0605

     ---------------------------------------- Majority
                      1010      1020      1030      1040
827  ---------------------------------------- mADAMTS-1
603  ---------------------------------------- hADAMTS-2
713  ACSKPCQGERK-RKLVCTRESD---QLTVSDQRCDRLPQP hADAMTS-3
892  ---------------------------------------- rADAMTS-4
804  ---------------------------------------- KIAA0688
852  QVSKPCGGGFQYTKYGCRRKSD---NKMVHRSFCEANKKP KIAA0366
633  ECSRTCGEGYQFRVVRCWKMLSPGFDSSVYSDLCEAAEAV KIAA0605

     ---------------------------------------- Majority
                      1050      1060      1070      1080
827  ---------------------------------------- mADAMTS-1
603  --------------------------------V-DFS---- hADAMTS-2
749  GHI-TEPCGT-DCDLR-WHVASRSECSAQCGL-GYRTLDI hADAMTS-3
892  ---------------------------------------- rADAMTS-4
804  ---------------------------------------- KIAA0688
889  KPI-RRMCNIQECTHPLWVAEEWEHCTKTCGSSGYQLRTV KIAA0366
673  RPEERKTCRNPACG-PQWEMSEWSECTAKCGERSVVTRDI KIAA0605

     --------------KVT----SSNTRPT-RXX-------- Majority
                      1090      1100      1110      1120
827  ------------KKKTE----SFNAIPTF-SE-------- mADAMTS-1
607  -------MQSSKERAT----TNITQPLLHAQ--------- hADAMTS-2
785  YCAKYSRLDGKTEKVDDGFCSSHPKPSNREKCSGECNTGG hADAMTS-3
892  ---------------------------------------- rADAMTS-4
804  --------------RPT----PSTPRPT-PQD-------- KIAA0688
928  RCLQ-PLLDGTNRSVHSKYCMGD-RPESRRPCNRVPCPAQ KIAA0366
712  RCSE-----------DEKLCDPNTRPVGEKNCTGPPCDRQ KIAA0605
```

Fig. 17G

```
      W V - G D W G E C S K T C G - G T Q R R X V - C R D - D G - V - - - S E C - K A  Majority
                    1130                1140                1150                1160
842   W V I E E W G E C S K T C G S G W Q R R V V Q C R D I N G H P - - A S E C A K E  mADAMTS-1
627   W V L G D W S E C S S T C G A G W Q R R T V E C R D P S G Q A - - S A T C N K A  hADAMTS-2
825   W R Y S A W T E C S K S C D G G T Q R R R A I C V N T R N D V L D D S K C T H Q  hADAMTS-3
892   - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  rADAMTS-4
817   W L - - - - - - - - - - - - - - - H R R A - - - - - - - - - - - - - - - - - Q I  KIAA0688
966   W K T G P W S E C S V T C G E G T E V R Q V L C R A G D H C D G E K P E S V R A  KIAA0366
741   W T V S D W G P C S G S C G Q G R T I R H V Y C K T S D G R V V P E S Q C Q M -  KIAA0605

      - - L K P L X X R P C - - - K S - - C P - - W - - - D W S - - - - - - - - C - -  Majority
                    1170                1180                1190                1200
880   - - V K P A S T R P C - - - A D L P C P - H W Q V G D W S P - - - - - - - C S K  mADAMTS-1
665   - - L K P E D A K P C - - - E S - - - - - - - - - - - - - - - - - - - - - - - -  hADAMTS-2
865   - - E K V T I Q R - C - - - S E F P C P - Q W K S G D W S E - - - - - - - C L V  hADAMTS-3
892   - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  rADAMTS-4
825   - - L E I L R R R P - - - - - - - - - - - - - - - - - W A - - - - - - - - - - -  KIAA0688
1006  C Q L P P C N D E P C L G D K S I F C Q - M E V L A R Y C S I P G Y N K L C C E  KIAA0366
780   - E T K P L A I H P C - G D K N - - C P A H W L A Q D W E R - - - - - - - C N T  KIAA0605

      T C G K - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - K K P T -  Majority
                    1210                1220                1230                1240
907   T C G K - - - - - - - - - - - - - - - - - - - - - - - - - - - - - G Y K K R T L  mADAMTS-1
676   - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  hADAMTS-2
891   T C G K - - - - - - - - - - - - - - - - - - - - - - - - - - - - - G H K H R Q V  hADAMTS-3
892   - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - K K P A X  rADAMTS-4
835   - - G R - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  KIAA0688
1045  S C S K R S S T L P P P Y L L E A A E T H D D V I S N P S D L P R S L V M P T S  KIAA0366
809   T C G R G V K K R L V L C M E L A N G K P Q T R S G P E C G L A K - - K P P E E  KIAA0605

      K V - - - - - - - - - - - - - - - - - - - - - S A - - - - - - - - - - - - - D T  Majority
                    1250                1260                1270                1280
918   K C V - - - - - - - - - - - - - - - - - - - - S H - - - - - - - - - - - - - D G  mADAMTS-1
676   - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  hADAMTS-2
902   W C Q F G E D R L N D R M C D P E V D A A A N S A - - - - - - - - - - - - - D T  hADAMTS-3
897   K V N - - - - - - - - - - - - - - - - - - - - S A - - - - - - - - - - - - - D T  rADAMTS-4
837   - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  KIAA0688
1085  L V P Y H S E T P A K K M S L S S I S S V G G P N A Y A A F R P N S K - - P D G  KIAA0366
847   S T C F - - E R P C F K W Y T S P W S E C T K T C G V G V R M R D V K C Y Q G T  KIAA0605
```

Fig. 17H

```
     D G L - Q E S P - - P - - - - - - - - - - - - P - - K P - - - - Q L C P L S Q C  Majority
                      1290                1300                1310                1320
925  G V L S N E S C - - D - - - - - - - - - - - - P L K K P K H Y I D F C T L T Q C  mADAMTS-1
676  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - Q L C P L .      hADAMTS-2
929  D G L Q E S S P - - P - - - - - - - - - - - I P I W K P S I F S H V - P S S R I  hADAMTS-3
904  D G L - Q E S S - - P - - - - - - - - - - - - P                                rADAMTS-4
837  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  KIAA0688
1123 A N L R Q R S A - - Q Q A G S K T V R L V T V P S S P P T K R V H L S S A S Q M  KIAA0366
885  D I V R G C D P L V K P V G R Q A C D L Q P C P T E P P D D S C Q D Q P G T N C  KIAA0605

     A - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -  Majority
                      1330                1340                1350                1360
951  S                                                                                mADAMTS-1
681                                                                                   hADAMTS-2
955  P                                                                                hADAMTS-3
912                                                                                   rADAMTS-4
837  K                                                                                KIAA0688
1161 A A A S F F A A S D S I G A S S Q A R T S K K D G K I I D N R R P T R S S T L E  KIAA0366
925  A L A I - - - - - - K V N L C G H W Y Y S K A C C R - - - S C R P P H S          KIAA0605

     -                                                                                Majority

951                                                                                   mADAMTS-1
681                                                                                   hADAMTS-2
955                                                                                   hADAMTS-3
912                                                                                   rADAMTS-4
837                                                                                   KIAA0688
1201 R                                                                                KIAA0366
951                                                                                   KIAA0605
```

Fig. 17I

Bovine ADAMTS 4 DNA

```
TTTAGGGAGG AGCAGTGTGA GGCCAAAAAT GGATATCAGT CTGATGCAAA AGGAGTCAAA    60
ACGTTTGTGG AATGGGTTCC CAAATATGCT GGTGTCCTGC CCGGAGACGT GTGCAAACTG   120
ACCTGCAGAG CTAAGGGCAC TGGCTACTAC GTGGTGTTCT CTCCAAAGGT GACCGATGGG   180
ACAGAGTGCA GGCCATACAG CAATTCCGTG TGTGTCCGGG GGAAGTGTGT GCGGACAGGC   240
TGTGACAGCA TCATTGGCTC GAAGCTGCAG TATGACAAAT GTGGCGTCTG TGGAGGAGAC   300
AACTCCAGTT GCACAAAGGT GGTCGGAACC TTCAATAAAA AAAGTAAGGG TTACACTGAC   360
GTCGTGAGGA TCCCCGAAGG GGCGACTCAC ATAAAAGTCC GACAGTTCAA AGCCAAAGAC   420
CAG                                                                 423
```

Fig. 18

Bovine ADAMTS 4 Protein

```
FREEQCEAKNGYQSDAKGVKTFVEWVPKYAGVLPGDVCKLTCRAKGTGYYVVFSPKVTDGTECRPYSNSVCVRGKCVRTG
CDSIIGSKLQYDKCGVCGGDNSSCTKVVGTFNKKSKGYTDVVRIPEGATHIKVRQFKAKDQ
```

Fig. 19

Bovine 0688 DNA

```
GGAAACCCTG GCCATTTGGA GCAACTACCT GGCCCTGAAG CTCCCCGATG GCTCCTATGC    60
CCTCAACGGT GAATACACGC TGATCCCGTC CCCCACAGAC GTGGTACTGC CCGGGGCCGT   120
CAGCCTGCGC TACAGCGGGG CCACTGCAGC CTCGGAGACA CTGTCAGGAC ACGGGCCCCT   180
GGCTGAGCCC TTAACGCTGC AGGTCCTAGT GGCTGGCAAC CCGCAGAACG CCCGCCTCAG   240
ATACAGCTTT TTCGTGCCGC GACCGCGACC GGTCCCCTCC ACGCCACGCC CCACTCCCCA   300
GGACTGGCTG CGCCGCAAGT CACAGATTCT GGAGATCCTC CGGCGGCGCT CCTGGGCCGG   360
CAGGAAATAA CCTCACCATC CCGGCTGCCC TTTCTGGGCA CCGGGGCCTC GGACTTAGCT   420
GGGTGAACGA GAGACCTCTG CAGCGGCCTC ACCCCGAGAC ATCGTGGGGG AGGGGCTTAG   480
TGAGCCCCGC CTCTCCTCCC CGCGCTACCG AGCAGGCTGG CCCTGCCGGG GTTTCCTGCC   540
CTGGATGGCT GGTGGATGGA AGGGGCTGGG AGATTGTCCC CTATCTAAAC TGCCCCCTCT   600
GCCCTGCTGG TCACAGGAGG GAGGGGGAAG GCAGGGA                             637
```

Fig. 20

Bovine KIAA 0688 Protein

ETLAIWSNYLALKLPDGSYALNGEYTLIPSPTDVVLPGAVSLRYSGATAASETLSGHGPLAEPLTLQVLVAGNPQNARLR
YSFFVPRPRPVPSTPRPTPQDWLRRKSQILEILRRRSWAGRK

Fig. 21

Human ADAMTS 5 DNA

```
ACTCACTATA GGGCTCGTGC GGCCGCCCGG GCAGGTATCT TTAAGCATCC CAGCATCCTC     60
AACCCCATCA ACATCGTTGT GGTCAAGGTG CTGCTTCTTA GAGATCGTGA CTCCGGGCCC    120
AAGGTCACCG GCAATGCGGC CCTGACGCTG CGCAACTTCT GTGCCTGGCA GAAGAAGCTG    180
AACAAAGTGA GTGACAAGCA CCCCGAGTAC TGGGACACTG CCATCCTCTT CACCAGGCAG    240
GACCTGTGTG GAGCCACCAC CTGTGACACC CTGGGCATGG CTGATGTGGG TACCATGTGT    300
GACCCCAAGA GAAGCTGCTC TGTCATTGAG GACGATGGGC TTCCATCAGC CTTCACCACT    360
GCCCACGAGC TGGGCCACGT GTTCAACATG CCCCATGACA ATGTGAAAGT CTGTGAGGAG    420
GTGTTTGGGA AGCTCCGAGC CAACCACATG ATGTCCCCGA CCCTCATCCA GATCGACCGT    480
GCCAACCCCT GGTCAGCCTG CAGTGCTGCC ATCATCACCG ACTTTCTGGA CAGCGGGCAC    540
GGTGACTGCC TCCTGGACCA ACCCAGCAAG CCCATCTTCC TGCCGAGNGA TCTGCCGGGC    600
GCCAGCTACA CCCTGAGCCA GCARTGCGAG CTGGCTTTTG GCGTGGGCTT CAAGCCCTGT    660
CCTTACATGC AGTACTGCAC CAAGCTGTGG TGCACCGGGA AGGCCAAGGG ACAGATGGTG    720
TGCCAAACCC GCCACTTCCC CTGGGCCGAT GGCACCAGTT GTGGCGAGGG CAAGTTCTGC    780
CTCAAAGGGG CCTGCGTGGA AARACACAAC CTCAACAAGC ACAGGGTGGA TGGTTCCTGG    840
GCCAAATGGG ATCCCTATGG CCCCTGCTCG CGCACATGTG GTGGGGGCGT GCAGCTGGCC    900
AGGAGGCAGN TGCACCAACC CCANCCCCTG CCAACNGGGG GCAAGTACTG CGAGGGAGTG    960
AGGGTGAAAT ACCGATCCTG CAACCTGGAG CCCTGCCCCA GCTCAGCCTC CGGAAAGAGC   1020
TTCCGGGAGG AGCAGTGTGA GGCTTTCAAC GGCTACAACC ACAGCACCAA CCGGCTCACT   1080
CTCGCCGTGG CATGGGTGCC CAAGTACTCC GGCGTGTCTC CCCGTGACAA GTGTAAGCTC   1140
ATC                                                                 1143
```

Fig. 22

Human ADAMTS 5 Protein

```
THYRARAAARAGIFKHPSILNPINIVVVKVLLLRDRDSGPKVTGNAALTLRNFCAWQKKLNKVSDKHPEYWDTAILFTRQ
DLCGATTCDTLGMADVGTMCDPKRSCSVIEDDGLPSAFTTAHELGHVFNMPHDNVKVCEEVFGKLRANHMMSPTLIQIDR
ANPWSACSAAIITDFLDSGHGDCLLDQPSKPIFLPXDLPGASYTLSQQCELAFGVGFKPCPYMQYCTKLWCTGKAKGQMV
CQTRHFPWADGTSCGEGKFCLKGACVEXHNLNKHRVDGSWAKWDPYGPCSRTCGGGVQLARRQXHQPXPLPTGGKYCEGV
RVKYRSCNLEPCPSSASGKSFREEQCEAFNGYNHSTNRLTLAVAWVPKYSGVSPRDKCKLI
```

Fig. 23

Rat ADAMTS 2 DNA

```
TCCGCCCTTC CGGGAGGAAC AGTGTGAAAA ATATAATGCC TACAACCACA CGGACCTGGA    60
TGGGAATTTC CTTCAGTGGG TCCCCAAATA CTCAGGAGTG TCCCCCCGAG ACCGATGCAA   120
ACTGTTTTGC AGAGCCCGTG GGAGGAGTGA GTTCAAAGTG TTTGAAACTA AGGTGATCGA   180
TGGCACTCTG TGCGGACCGG ATACTCTGGC CATCTGTGTG CGGGGACAGT GCGTTAAGGC   240
TGGCTGTGAC CATGTGGTGA ACTCACCTAA GAAGCTGGAC AAGTGCGGTA TCTGTGG      297
```

Fig. 24

Rat ADAMTS 2 Protein

```
PPFREEQCEKYNAYNHTDLDGNFLQWVPKYSGVSPRDRCKLFCRARGRSEFKVFETKVIDGTLCGPDTLAICVRGQCVKA
GCDHVVNSPKKLDKCGIC
```

Fig. 25

Rat ADAMTS 3 DNA

```
CCCCTGGATG TGGTCAAAGT GCAGTCGGAA GTACATCACC GAGTTCTTAG ACACTGGGTA    60
TGGAGAGTGC TTGTTAAATG AACCTCAATC CAGGACCTAT CCTTTGCCTT CCCAACTGCC   120
CGGCCTTCTC TACAACGTGA ATAAACAATG TGAACTGATT TTTGGACCAG GCTCTCAAGT   180
GTGCCCATAT ATGATGCAGT GCAGACGGCT CTGGTGCAAT AACGTGGATG GAGCACACAA   240
AGGCTGCAGG ACTCAGCACA CGCCCTGGGC AGATGGAACC GAGTGTGAGC CTGGAAAGCA   300
CTGCAAGTTT GGATTCTGTG TTCCCAAAGA AATGGAGGGC CCTGCAATTG ATGGATCCTG   360
GGGAAGTTGG AGTCACTTTG GGGCCTGCTC AAGAACATGT GGAGGAGGCA TCAGAACAGC   420
CATCAGAGAG TGCAACAGAC CAGAGCCAAA AAATGGTGGG AGGTACTGTG TAGGGAGGAG   480
AATRAAGTTC AAATCCTGCA ACACCGAGCC CTGCCCGAAG CACAAGCGAG ACTTCCGTGA   540
GGAGCAGTGT GCTTACTTTG ACGGCAAGCA TTTCAACATC AATGGTCTGC TGCCCAGTGT   600
ACGCTGGGTC CCTAAGTACA GTGGAATTTT GATGAAGGAC CGATGCAAGT TGTTCTGCAG   660
AGTGGCAGGA AACACAGCCT ACTACCAGCT TCGAGACAGA GTGATTGACG GAACCCCCTG   720
TGGCCAGGAC ACAAATGACA TCTGTGTCCA AGGCCTTTGC CGGCAAGCTG GATGTGATCA   780
TACTTTAAAC TCAAAGGCCC GGAAAGATAA ATGTGGGATT TGT                      823
```

Fig. 26

Rat ADAMTS 3 Protein

```
PWMWSKCSRKYITEFLDTGYGECLLNEPQSRTYPLPSQLPGLLYNVNKQCELIFGPGSQVCPYMMQCRRLWCNNVDGAHK
GCRTQHTPWADGTECEPGKHCKFGFCVPKEMEGPAIDGSWGSWSHFGACSRTCGGGIRTAIRECNRPEPKNGGRYCVGRR
XKFKSCNTEPCPKHKRDFREEQCAYFDGKHFNINGLLPSVRWVPKYSGILMKDRCKLFCRVAGNTAYYQLRDRVIDGTPC
GQDTNDICVQGLCRQAGCDHTLNSKARKDKCGIC
```

Fig. 27

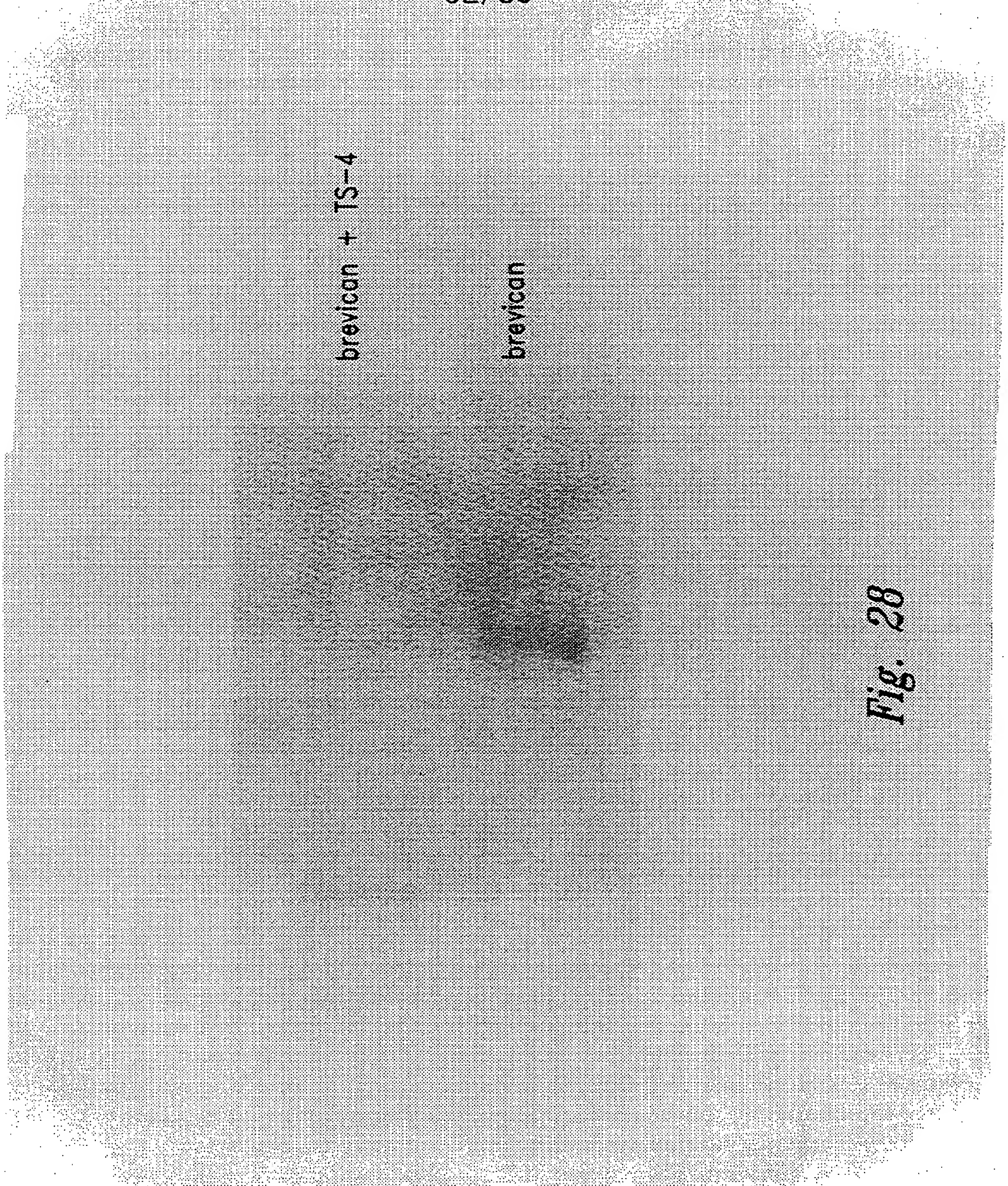


Fig. 28

MQFVSWATLLTLLVRDLAEMGSPDAAAAVRKDRLHPRQVKLLETLGEYEIVSPIRVNALGEPFPTNVHFKRTRRSINSAT

DPWPAFASSSSSSTSSQAHYRLSAFGQQFLFNLTANAGFIAPLFTVTLLGTPGVNQTKFYSEEEAELKHCFYKGYVNTNS

cysteine switch*

EHTAVISLCSGMLGTFRSHDGDYFIEPLQSMDEQEDEEEQNKPHIIYRRSAPQREPSTGRHACDTSEHKNRHSKDKKKTR

potential furin cleavage sites metalloprotease domain

ARKWGERINLAGDVAALNSGLATEAFSAYGNKTDNTREKRTHRRTKRFLSYPRFVEVLVVADNRMVSYHGENLQHYILTL

MSIVASIYKDPSIGNLINIVIVNLIVIHNEQDGPSISFNAQTTLKNLCQWQHSKNSPGGIHHDTAVLLTRQDICRAHDKC

Zn binding Met turn

DTLGLAELGTICDPYRSCSISEDSGLSTAFTIAHELGHVFNMPHDDNNKCKEEGVKSPQHVMAPTLNFYTNPWMWSKCSR

disintegrin-like domain

KYITEFLDTGYGECLLNEPESRPYPLPVQLPGILYNVNKQCELIFGPGSQVCPYMMQCRRLWCNNVNGVHKGCRTQHTPW

TSP 1 motif

ADGTECEPGKHCKYGFCVPKEMDVPVTDGSWGSWSPFGTCSRTCGGGIKTAIRECNRPEPKNGGKYCVGRRMKFKSCNTE

spacer region

PCLKQKRDFRDEQCAHFDGKHFNINGLLPNVRWVPKYSGILMKDRCKLFCRVAGNTAYYQLRDRVIDGTPCGQDTNDICV

QGLCRQAGCDHVLNSKARRDKCGVCGGDNSSCKTVAGTFNTVHYGYNTVVRIPAGATNIDVRQHSFSGETDDDNYLALSS

SKGEFLLNGNFVVTMAKREIRIGNAVVEYSGSETAVERINSTDRIEQELLLQVLSVGKLYNPDVRYSFNIPIEDKPQQFY

TSP1-like submotif 1 TSP1-like submotif 2

WNSHGPWQACSKPCQGERKRKLVCTRESDQLTVSDQRCDRLPQPGHITEPCGTDCDLRWHVASRSECSAQCGLGYRTLDI

TSP1-like submotif 3

YCAKYSRLDGKTEKVDDGFCSSHPKPSNREKCSGECNTGGWRYSAWTECSKSCDGGTQRRRAICVNTRNDVLDDSKCTHQ

EKVTIQRCSEFPCPQWKSGDWSEVRWEGCYFP

Fig. 29

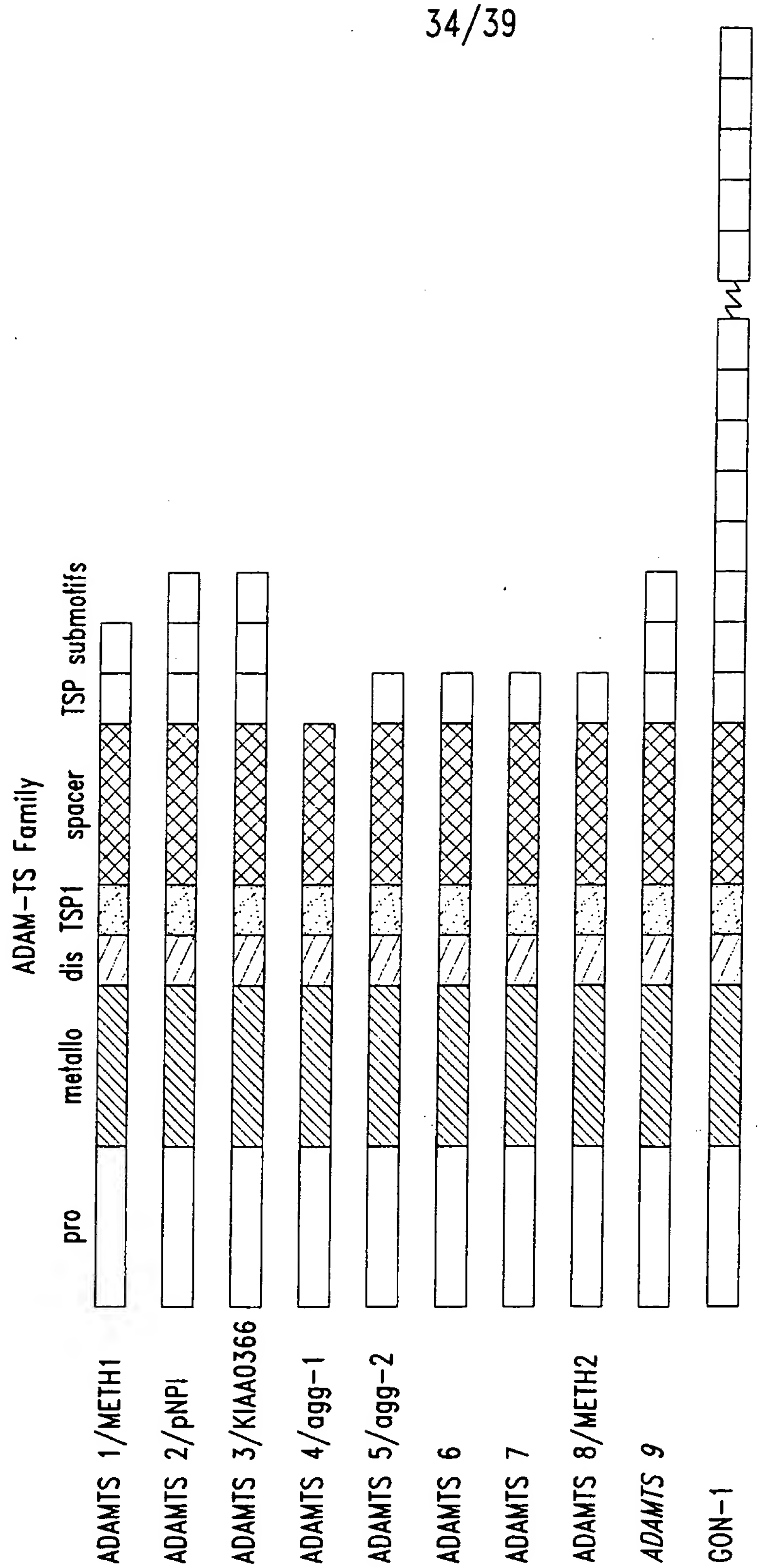

ADAM-TS Family
pro
metallo
dis
TSP1
spacer
TSP submotifs
ADAMTS 1/METH1
ADAMTS 2/pNPI
ADAMTS 3/KIAA0366
ADAMTS 4/agg-1
ADAMTS 5/agg-2
ADAMTS 6
ADAMTS 7
ADAMTS 8/METH2
ADAMTS 9
GON-1

Fig. 30A

CONSENSUS	HEXXHXXGXXHD
Fertilin α	HELGHNLGIRHD
ADAM 17/TACE	HELGHNFGAEHD
ADAM 10/Kuz	HEIGHNFGSPHD
ADAMTS 1	HELGHVFNMPHD
ADAMTS 2	HETGHVLGMEHD
ADAMTS 4	HELGHVFNMLHD
ADAMTS 5	HEIGHLLGLSHD
ADAMTS 9	HELGHVFNMPHD
GON-1	HELGHVFSIPHD

Fig. 30B

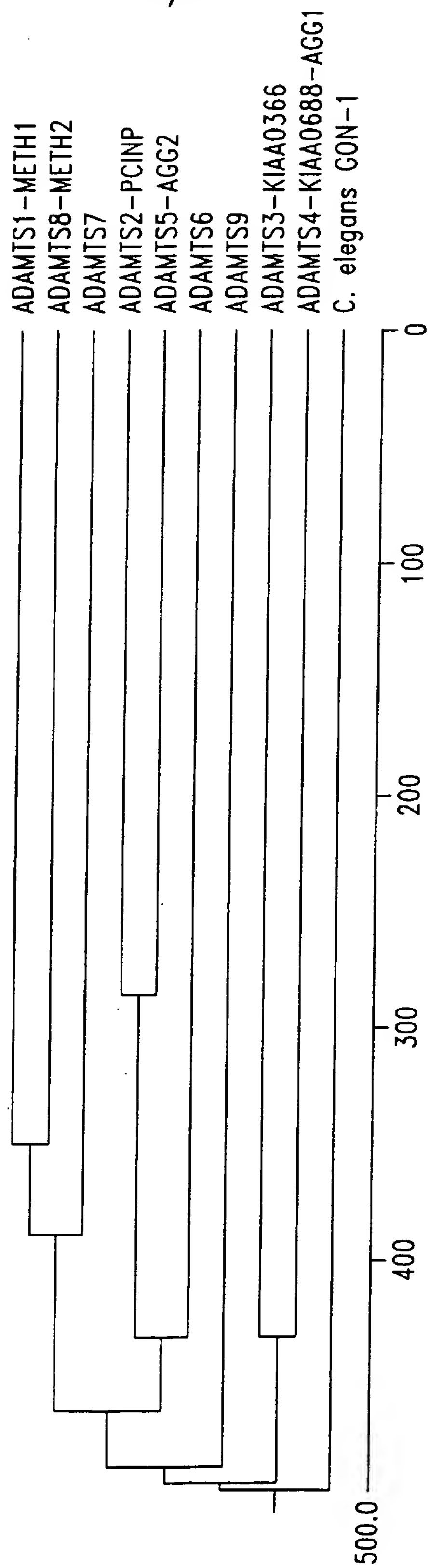

ADAMTS1-METH1
ADAMTS8-METH2
ADAMTS7
ADAMTS2-PCINP
ADAMTS5-AGG2
ADAMTS6
ADAMTS9
ADAMTS3-KIAA0366
ADAMTS4-KIAA0688-AGG1
C. elegans GON-1
0
100
200
300
400
500.0

Fig. 30C

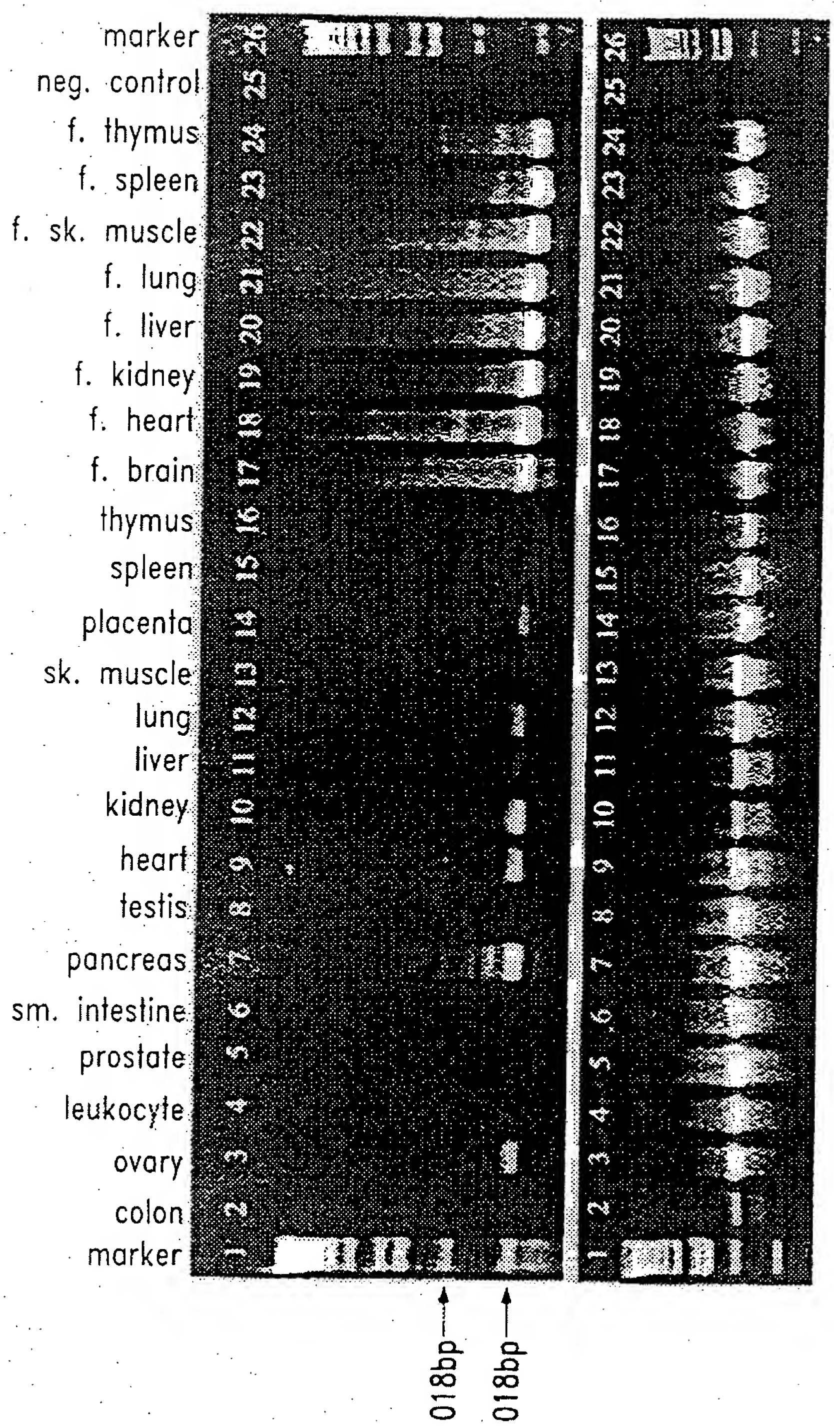

marker
neg. control
f. thymus
f. spleen
f. sk. muscle
f. lung
f. liver
f. kidney
f. heart
f. brain
thymus
spleen
placenta
sk. muscle
lung
liver
kidney
heart
testis
pancreas
sm. intestine
prostate
leukocyte
ovary
colon
marker
26
25
24
23
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
1018bp
1018bp

Fig. 31

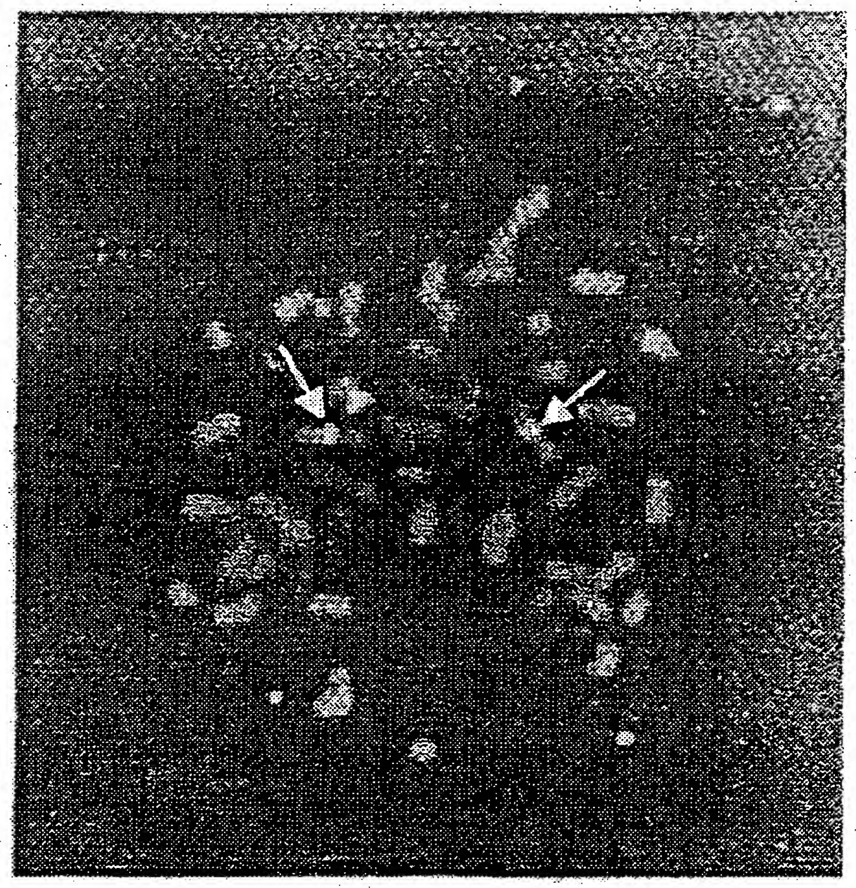
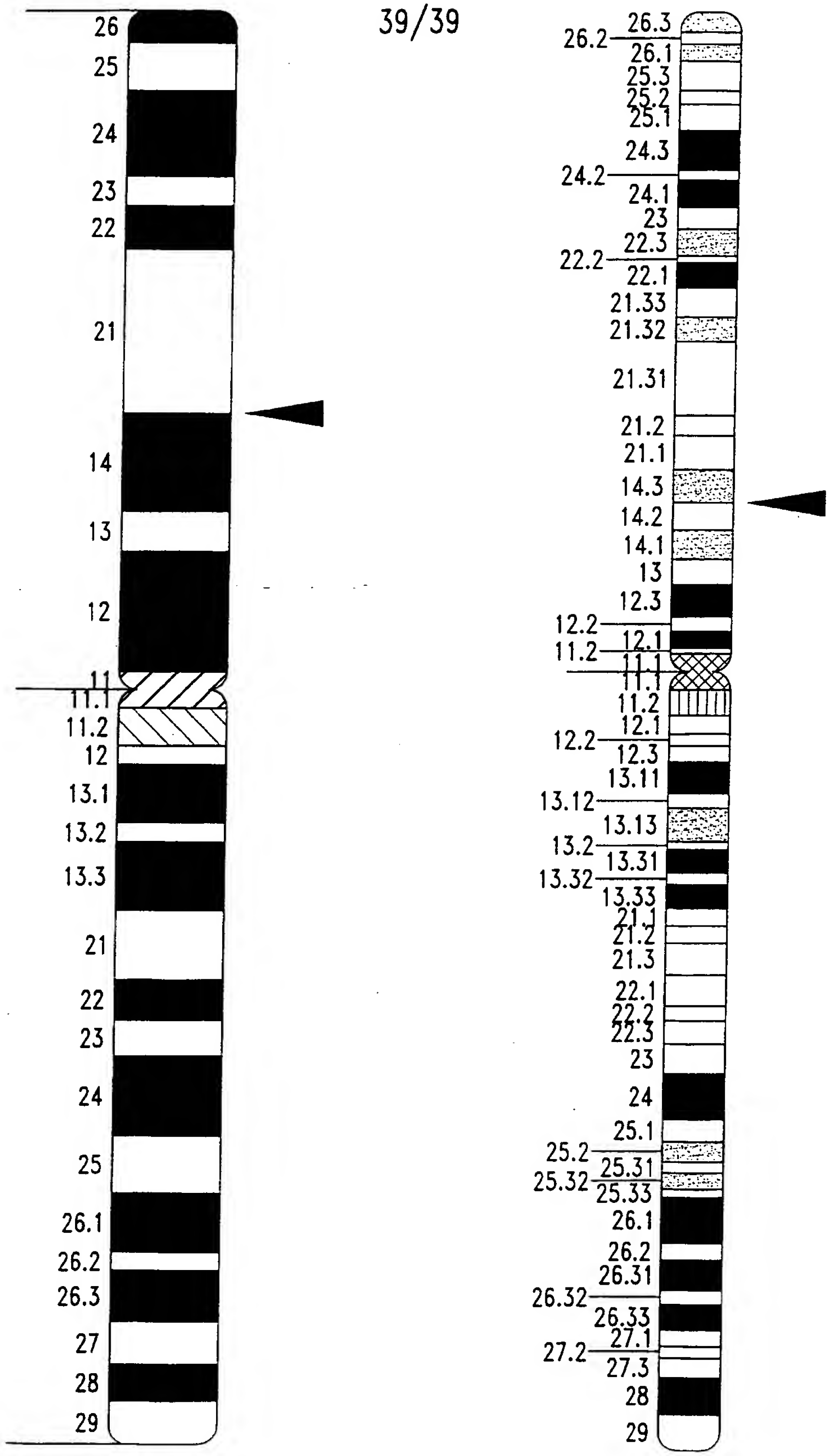


Fig. 32A


26
25
24
23
22
21
14
13
12
11
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11.2
12
13.1
13.2
13.3
21
22
23
24
25
26.1
26.2
26.3
27
28
29
26.3
26.2
26.1
25.3
25.2
25.1
24.3
24.2
24.1
23
22.3
22.2
22.1
21.33
21.32
21.31
21.2
21.1
14.3
14.2
14.1
13
12.3
12.2
12.1
11.2
11.1
11.1
11.2
12.1
12.2
12.3
13.11
13.12
13.13
13.2
13.31
13.32
13.33
21.1
21.2
21.3
22.1
22.2
22.3
23
24
25.1
25.2
25.31
25.32
25.33
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26.2
26.31
26.32
26.33
27.1
27.2
27.3
28
29

Fig. 32B

SEQUENCE LISTING

<110> Neurocrine Biosciences, Inc.
Kelner, Gregory S.
Clark, Melody
Maki, Richard A.

<120> METALLOPROTEINASES AND METHODS OF USE THEREFOR

<130> 690068.453PC

<140> PCT
<141> 2000-03-08

<160> 51

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His Ile Leu Thr Leu Met Ser Val Ala Ala Arg Ile Tyr Lys His Pro
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Ser Ile Lys Asn Ser Ile Asn Leu Met Val Val Lys Val Leu Ile Val
    50                  55                  60
Glu Asp Glu Lys Trp Gly Pro Glu Val Ser Asp Asn Gly Gly Leu Thr
65                  70                  75                  80
Leu Arg Asn Phe Cys Asn Trp Gln Arg Arg Phe Asn Gln Pro Ser Asp
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Arg His Pro Glu His Tyr Asp Thr Ala Ile Leu Leu Thr Arg Gln Asn
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Phe Cys Gly Gln Glu Gly Leu Cys Asp Thr Leu Gly Val Ala Asp Ile
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Gly Leu Gln Ala Ala His Thr Leu Ala His Glu Leu Gly His Val Leu
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Met Gly Lys His His Val Met Ala Pro Leu Phe Val His Leu Asn Gln
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225                 230                 235                 240
Gln Gln Cys Arg Gln Ile Phe Gly Pro Asp Phe Arg His Cys Pro Asn
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Glu Glu Cys Pro Pro Asp Gly Lys Ser Phe Arg Glu Gln Gln Cys Glu
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Ser His Pro Gly Val Gln Asn Asp Gly Asn Tyr Leu Ala Leu Lys Thr
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Asp Gln Arg Gln Trp Glu Glu Thr Gln Glu Arg Gly His Leu Gln Pro
    50                  55                  60
Leu Ala Arg Gln Arg Arg Ser Ser Gly Leu Val Gln Asn Ile Asp Gln
65                  70                  75                  80
Leu Tyr Ser Gly Gly Gly Lys Val Gly Tyr Leu Val Tyr Ala Gly Gly
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Gly Gly Ile Val Thr Ala Gly Gly Leu Ser Ala Ser Ser Gly His Arg
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Ser Glu Arg Val Tyr Gly Asp Gly Ser Ser Arg Ile Leu His Val Tyr
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Thr Arg Glu Gly Phe Ser Phe Glu Ala Leu Pro Pro Arg Thr Ser Cys
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Glu Thr Pro Ala Ser Pro Ser Gly Ala Gln Glu Ser Pro Ser Val His
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Ser Ala Phe Ser Pro Ala Gly Asn Ala Gly Pro Gln Thr Trp Trp Arg
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675 680 685
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690 695 700
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785 790 795 800
Thr Val Met Asn Tyr Ser Gly Trp Ser His Arg Asp Asp Phe Leu His
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820 825 830
Ala Thr Asp Pro Thr Lys Ala Leu Asp Val Arg Tyr Ser Phe Phe Val

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<213> Homo sapien

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Ser Pro Thr Ser Asn Ser Leu Glu Gly Gly Thr Asp Ala Thr Ala Phe
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Trp Trp Gly Glu Trp Thr Lys Trp Thr Ala Phe Ser Arg Ser Cys Gly
    50                  55                  60
Gly Gly Val Thr Ser Gln Glu Arg His Cys Leu Gln Gln Arg Arg Lys
65                  70                  75                  80
Ser Val Pro Gly Pro Gly Asn Arg Thr Cys Thr Gly Thr Ser Lys Arg
                85                  90                  95
Tyr Gln Leu Cys Arg Val Gln Glu Cys Pro Pro Asp Gly Arg Ser Phe
            100                 105                 110
Arg Glu Glu Gln Cys Val Ser Phe Asn Ser His Val Tyr Asn Gly Arg
        115                 120                 125
Thr His Gln Trp Lys Pro Leu Tyr Pro Asp Asp Tyr Val His Ile Ser
    130                 135                 140
Ser Lys Pro Cys Asp Leu His Cys Thr Thr Val Asp Gly Gln Arg Gln
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Leu Met Val Pro Ala Arg Asp Gly Thr Ser Cys Lys Leu Thr Asp Leu
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Arg Gly Val Cys Val Ser Gly Lys Cys Glu Pro Ile Gly Cys Asp Gly
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Val Leu Phe Ser Thr His Thr Leu Asp Lys Cys Gly Ile Cys Gln Gly
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225                     230                     235                     240
Asp Ile Gln Ile Val Glu Arg Lys Lys Ser Ala Asp Val Leu Ala Leu
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Ala Asp Glu Ala Gly Tyr Tyr Phe Phe Asn Gly Asn Tyr Lys Val Asp
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Ser Pro Lys Asn Phe Asn Ile Ala Gly Thr Val Val Lys Tyr Arg Arg
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Pro Met Asp Val Tyr Glu Thr Gly Ile Glu Tyr Ile Val Ala Gln Gly
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Pro Thr Asn Gln Gly Leu Asn Val Met Val Trp Asn Gln Asn Gly Lys
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Ser Pro Ser Ile Thr Phe Glu Tyr Thr Leu Leu Gln Pro Pro His Glu
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Ser Arg Pro Gln Pro Ile Tyr Tyr Gly Phe Ser Glu Ser Ala Glu Ser
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Gln Gly Leu Asp Gly Ala Gly Leu Met Gly Phe Ile Pro His Asn Gly
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Leu Phe Gly His Pro Gly Leu Asp Met Glu Leu Gly Pro Ser Gln Gly
385                     390                     395                     400
Gln Glu Thr Asn Glu Val Cys Glu Gln Ala Gly Gly Gly Ala Cys Glu
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Gly Pro Pro Arg Gly Lys Gly Phe Arg Asp Arg Asn Val Thr Gly Thr
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Pro Leu Thr Gly Asp Lys Asp Asp Glu Glu Val Asp Thr His Phe Ala
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Phe Asp Ser Ser Val Tyr Ser Asp Leu Cys Glu Ala Ala Glu Ala Val
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675 680 685
Trp Glu Met Ser Glu Trp Ser Glu Cys Thr Ala Lys Cys Gly Glu Arg
690 695 700
Ser Val Val Thr Arg Asp Ile Arg Cys Ser Glu Asp Glu Lys Leu Cys
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Cys Asp Arg Gln Trp Thr Val Ser Asp Trp Gly Pro Cys Ser Gly Ser
740 745 750
Cys Gly Gln Gly Arg Thr Ile Arg His Val Tyr Cys Lys Thr Ser Asp
755 760 765
Gly Arg Val Val Pro Glu Ser Gln Cys Gln Met Glu Thr Lys Pro Leu
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Ala Ile His Pro Cys Gly Asp Lys Asn Cys Pro Ala His Trp Leu Ala
785 790 795 800
Gln Asp Trp Glu Arg Cys Asn Thr Thr Cys Gly Arg Gly Val Lys Lys
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835 840 845
Cys Phe Glu Arg Pro Cys Phe Lys Trp Tyr Thr Ser Pro Trp Ser Glu
850 855 860
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865 870 875 880
Tyr Gln Gly Thr Asp Ile Val Arg Gly Cys Asp Pro Leu Val Lys Pro
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Val Gly Arg Gln Ala Cys Asp Leu Gln Pro Cys Pro Thr Glu Pro Pro
900 905 910
Asp Asp Ser Cys Gln Asp Gln Pro Gly Thr Asn Cys Ala Leu Ala Ile
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Glu Gly Arg Tyr Leu Ser His Thr Leu Ser Ala Ser His Lys Lys Arg
50 55 60
Ser Ala Arg Asp Val Ser Ser Asn Pro Glu Gln Leu Phe Phe Asn Ile
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Thr Ala Phe Gly Lys Asp Phe His Leu Arg Leu Lys Pro Asn Thr Gln
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Val Gly Asp Ile Val Asp Ile Pro Gly Thr Ser Val Ala Ile Ser Asn
145                 150                 155                 160
Cys Asp Gly Leu Ala Gly Met Ile Lys Ser Asp Asn Glu Glu Tyr Phe
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Ile Glu Pro Leu Glu Arg Gly Lys Gln Met Glu Glu Glu Lys Gly Arg
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Ile His Val Val Tyr Lys Arg Ser Ala Val Glu Gln Ala Pro Ile Asp
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Met Ser Lys Asp Phe His Tyr Arg Glu Ser Asp Leu Glu Gly Leu Asp
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Asp Leu Gly Thr Val Tyr Gly Asn Ile His Gln Gln Leu Asn Glu Thr
225                 230                 235                 240
Met Arg Arg Arg Arg His Ala Gly Glu Asn Asp Tyr Asn Ile Glu Val
                245                 250                 255
Leu Leu Gly Val Asp Asp Ser Val Val Arg Phe His Gly Lys Glu His
            260                 265                 270
Val Gln Asn Tyr Leu Leu Thr Leu Met Asn Ile Val Asn Glu Ile Tyr
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His Asp Glu Ser Leu Gly Val His Ile Asn Val Val Leu Val Arg Met
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Ile Met Leu Gly Tyr Ala Lys Ser Ile Ser Leu Ile Glu Arg Gly Asn
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Pro Ser Arg Ser Leu Glu Asn Val Cys Arg Trp Ala Ser Gln Gln Gln
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Arg Ser Asp Leu Asn His Ser Glu His His Asp His Ala Ile Phe Leu
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Thr Val Arg Leu Val Thr Val Pro Ser Ser Pro Pro Thr Lys Arg Val
1140 1145 1150
His Leu Ser Ser Ala Ser Gln Met Ala Ala Ala Ser Phe Phe Ala Ala
1155 1160 1165
Ser Asp Ser Ile Gly Ala Ser Ser Gln Ala Arg Thr Ser Lys Lys Asp
1170 1175 1180
Gly Lys Ile Ile Asp Asn Arg Arg Pro Thr Arg Ser Ser Thr Leu Glu
1185 1190 1195 1200
Arg

<210> 9
<211> 2868
<212> DNA
<213> Homo sapien

<400> 9
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cgcagcgccc cccagagaga gccctcaaca ggaaggcatg catgtgacac ctcagaacac 240
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aacctggctg gtgacgtagc agcattaaac agcggcttag caacagaggc attttctgct 360
tatggtaata agacggacaa cacaagagaa aagaggaccc acagaaggac aaaacgtttt 420
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<210> 10
<211> 958
<212> PRT
<213> Homo sapien

<400> 10
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Gly Asp Tyr Phe Ile Glu Pro Leu Gln Ser Met Asp Glu Gln Glu Asp
35 40 45
Glu Glu Glu Gln Asn Lys Pro His Ile Ile Tyr Arg Arg Ser Ala Pro
50 55 60
Gln Arg Glu Pro Ser Thr Gly Arg His Ala Cys Asp Thr Ser Glu His
65 70 75 80
Lys Asn Arg His Ser Lys Asp Lys Lys Lys Thr Arg Ala Arg Lys Trp
85 90 95
Gly Glu Arg Ile Asn Leu Ala Gly Asp Val Ala Ala Leu Asn Ser Gly
100 105 110
Leu Ala Thr Glu Ala Phe Ser Ala Tyr Gly Asn Lys Thr Asp Asn Thr
115 120 125
Arg Glu Lys Arg Thr His Arg Arg Thr Lys Arg Phe Leu Ser Tyr Pro
130 135 140

Arg Phe Val Glu Val Leu Val Val Ala Asp Asn Arg Met Val Ser Tyr
145   150   155   160
His Gly Glu Asn Leu Gln His Tyr Ile Leu Thr Leu Met Ser Ile Asp
                165   170   175
Gly Pro Ser Ile Ser Phe Asn Ala Gln Thr Thr Leu Lys Asn Leu Cys
            180   185   190
Gln Trp Gln His Ser Lys Asn Ser Pro Gly Gly Ile His His Asp Thr
        195   200   205
Ala Val Leu Leu Thr Arg Gln Asp Ile Cys Arg Ala His Asp Lys Cys
    210   215   220
Asp Thr Leu Gly Leu Ala Glu Leu Gly Thr Ile Cys Asp Pro Tyr Arg
225   230   235   240
Ser Cys Ser Ile Ser Glu Asp Ser Gly Leu Ser Thr Ala Phe Thr Ile
                245   250   255
Ala His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Asn Asn
            260   265   270
Lys Cys Lys Glu Glu Gly Val Lys Ser Pro Gln His Val Met Ala Pro
        275   280   285
Thr Leu Asn Phe Tyr Thr Asn Pro Trp Met Trp Ser Lys Cys Ser Arg
    290   295   300
Lys Tyr Ile Thr Glu Phe Leu Asp Thr Gly Tyr Gly Glu Cys Leu Leu
305   310   315   320
Asn Glu Pro Glu Ser Arg Pro Tyr Pro Leu Pro Val Gln Leu Pro Gly
                325   330   335
Ile Leu Tyr Asn Val Asn Lys Gln Cys Glu Leu Ile Phe Gly Pro Gly
            340   345   350
Ser Gln Val Cys Pro Tyr Met Met Gln Cys Arg Arg Leu Trp Cys Asn
        355   360   365
Asn Val Asn Gly Val His Lys Gly Cys Arg Thr Gln His Thr Pro Trp
    370   375   380
Ala Asp Gly Thr Glu Cys Glu Pro Gly Lys His Cys Lys Tyr Gly Phe
385   390   395   400
Cys Val Pro Lys Glu Met Asp Val Pro Val Thr Asp Gly Ser Trp Gly
                405   410   415
Ser Trp Ser Pro Phe Gly Thr Cys Ser Arg Thr Cys Gly Gly Gly Ile
            420   425   430
Lys Thr Ala Ile Arg Glu Cys Asn Arg Pro Glu Pro Lys Asn Gly Gly
        435   440   445
Lys Tyr Cys Val Gly Arg Arg Met Lys Phe Lys Ser Cys Asn Thr Glu
    450   455   460
Pro Cys Leu Lys Gln Lys Arg Asp Phe Arg Asp Glu Gln Cys Ala His
465   470   475   480
Phe Asp Gly Lys His Phe Asn Ile Asn Gly Leu Leu Pro Asn Val Arg
                485   490   495
Trp Val Pro Lys Tyr Ser Gly Ile Leu Met Lys Asp Arg Cys Lys Leu
            500   505   510
Phe Cys Arg Val Ala Gly Asn Thr Ala Tyr Tyr Gln Leu Arg Asp Arg
        515   520   525
Val Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val
    530   535   540
Gln Gly Leu Cys Arg Gln Ala Gly Cys Asp His Val Leu Asn Ser Lys
545   550   555   560
Ala Arg Arg Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys
                565   570   575
Lys Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr

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Val Val Arg Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Arg Gln His
            595                 600                 605
Ser Phe Ser Gly Glu Thr Asp Asp Asp Asn Tyr Leu Ala Leu Ser Ser
    610                 615                 620
Ser Lys Gly Glu Phe Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala
625                 630                 635                 640
Lys Arg Glu Ile Arg Ile Gly Asn Ala Val Val Glu Tyr Ser Gly Ser
                645                 650                 655
Glu Thr Ala Val Glu Arg Ile Asn Ser Thr Asp Arg Ile Glu Gln Glu
            660                 665                 670
Leu Leu Leu Gln Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val
        675                 680                 685
Arg Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr
    690                 695                 700
Trp Asn Ser His Gly Pro Trp Gln Ala Cys Ser Lys Pro Cys Gln Gly
705                 710                 715                 720
Glu Arg Lys Arg Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr
                725                 730                 735
Val Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr
            740                 745                 750
Glu Pro Cys Gly Thr Asp Cys Asp Leu Arg Trp His Val Ala Ser Arg
        755                 760                 765
Ser Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile
    770                 775                 780
Tyr Cys Ala Lys Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp
785                 790                 795                 800
Asp Gly Phe Cys Ser Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys
                805                 810                 815
Ser Gly Glu Cys Asn Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu
            820                 825                 830
Cys Ser Lys Ser Cys Asp Gly Gly Thr Gln Arg Arg Arg Ala Ile Cys
        835                 840                 845
Val Asn Thr Arg Asn Asp Val Leu Asp Asp Ser Lys Cys Thr His Gln
    850                 855                 860
Glu Lys Val Thr Ile Gln Arg Cys Ser Glu Phe Pro Cys Pro Gln Trp
865                 870                 875                 880
Lys Ser Gly Asp Trp Ser Glu Cys Leu Val Thr Cys Gly Lys Gly His
                885                 890                 895
Lys His Arg Gln Val Trp Cys Gln Phe Gly Glu Asp Arg Leu Asn Asp
            900                 905                 910
Arg Met Cys Asp Pro Glu Val Asp Ala Ala Ala Asn Ser Ala Asp Thr
        915                 920                 925
Asp Gly Leu Gln Glu Ser Ser Pro Pro Ile Pro Ile Trp Lys Pro Ser
    930                 935                 940
Ile Phe Ser His Val Pro Ser Ser Arg Ile Pro Phe Ile Gly
945                 950                 955
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<210> 11
<211> 4303
<212> DNA
<213> Homo sapien

<400> 11

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gagagtttgg agaagccaga cccctgggca cctctcccaa gcccaaggac taagttttct      240
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ccaagccccc aggctacaga gaggagcttt ccaaagctag ggtgtggagg acttggtgcc      360
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<210> 12
<211> 840
<212> PRT
<213> Homo sapien

<400> 12

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Trp Leu Val Trp Leu Leu Leu Leu Leu Leu Ala Ser Leu Leu Pro Ser
        35                  40                  45
Ala Arg Leu Ala Ser Pro Leu Pro Arg Glu Glu Glu Ile Val Phe Pro
    50                  55                  60
Glu Lys Leu Asn Gly Ser Val Leu Pro Gly Ser Gly Thr Pro Ala Arg
65                  70                  75                  80
Leu Leu Cys Arg Leu Gln Ala Phe Gly Glu Thr Leu Leu Leu Glu Leu
                85                  90                  95
Glu Gln Asp Ser Gly Val Gln Val Glu Gly Leu Thr Val Gln Tyr Leu
            100                 105                 110
Gly Gln Ala Pro Glu Leu Leu Gly Gly Ala Glu Pro Gly Thr Tyr Leu
        115                 120                 125
Thr Gly Thr Ile Asn Gly Asp Pro Glu Ser Val Ala Ser Leu His Trp
    130                 135                 140
Asp Gly Gly Ala Leu Leu Gly Val Leu Gln Tyr Arg Gly Ala Glu Leu
145                 150                 155                 160
His Leu Gln Pro Leu Glu Gly Gly Thr Pro Asn Ser Ala Gly Gly Pro
                165                 170                 175
Gly Ala His Ile Leu Arg Arg Lys Ser Pro Ala Ser Gly Gln Gly Pro
            180                 185                 190
Met Cys Asn Val Lys Ala Pro Leu Gly Ser Pro Ser Pro Arg Pro Arg
        195                 200                 205
Arg Ala Lys Arg Phe Ala Ser Leu Ser Arg Phe Val Glu Thr Leu Val
    210                 215                 220
Val Ala Asp Asp Lys Met Ala Ala Phe His Gly Ala Gly Leu Lys Arg
225                 230                 235                 240
Tyr Leu Leu Thr Val Met Ala Ala Ala Ala Lys Ala Phe Lys His Pro
                245                 250                 255
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Ser Ile Arg Asn Pro Val Ser Leu Val Val Thr Arg Leu Val Ile Leu
260 265 270
Gly Ser Gly Glu Glu Gly Pro Gln Val Gly Pro Ser Ala Ala Gln Thr
275 280 285
Leu Arg Ser Phe Cys Ala Trp Gln Arg Gly Leu Asn Thr Pro Glu Asp
290 295 300
Ser Asp Pro Asp His Phe Asp Thr Ala Ile Leu Phe Thr Arg Gln Asp
305 310 315 320
Leu Cys Gly Val Ser Thr Cys Asp Thr Leu Gly Met Ala Asp Val Gly
325 330 335
Thr Val Cys Asp Pro Ala Arg Ser Cys Ala Ile Val Glu Asp Asp Gly
340 345 350
Leu Gln Ser Ala Phe Thr Ala Ala His Glu Leu Gly His Val Phe Asn
355 360 365
Met Leu His Asp Asn Ser Lys Pro Cys Ile Ser Leu Asn Gly Pro Leu
370 375 380
Ser Thr Ser Arg His Val Met Ala Pro Val Met Ala His Val Asp Pro
385 390 395 400
Glu Glu Pro Trp Ser Pro Cys Ser Ala Arg Phe Ile Thr Asp Phe Leu
405 410 415
Asp Asn Gly Tyr Gly His Cys Leu Leu Asp Lys Pro Glu Ala Pro Leu
420 425 430
His Leu Pro Val Thr Phe Pro Gly Lys Asp Tyr Asp Ala Asp Arg Gln
435 440 445
Cys Gln Leu Thr Phe Gly Pro Asp Ser Arg His Cys Pro Gln Leu Pro
450 455 460
Pro Pro Cys Ala Ala Leu Trp Cys Ser Gly His Leu Asn Gly His Ala
465 470 475 480
Met Cys Gln Thr Lys His Ser Pro Trp Ala Asp Gly Thr Pro Cys Gly
485 490 495
Pro Ala Gln Ala Cys Met Gly Gly Arg Cys Leu His Met Asp Gln Leu
500 505 510
Gln Asp Phe Asn Ile Pro Gln Ala Gly Gly Trp Gly Pro Trp Gly Pro
515 520 525
Trp Gly Asp Cys Ser Arg Thr Cys Gly Gly Gly Val Gln Phe Ser Ser
530 535 540
Arg Asp Cys Thr Arg Pro Val Pro Arg Asn Gly Gly Lys Tyr Cys Glu
545 550 555 560
Gly Arg Arg Thr Arg Phe Arg Ser Cys Asn Thr Glu Asp Cys Pro Thr
565 570 575
Gly Ser Ala Leu Thr Phe Arg Glu Glu Gln Cys Ala Ala Tyr Asn His
580 585 590
Arg Thr Asp Leu Phe Lys Ser Phe Pro Gly Pro Met Asp Trp Val Pro
595 600 605
Arg Tyr Thr Gly Val Ala Pro Gln Asp Gln Cys Lys Leu Thr Cys Gln
610 615 620
Ala Arg Ala Leu Gly Tyr Tyr Tyr Val Leu Glu Pro Arg Val Val Asp
625 630 635 640
Gly Thr Pro Cys Ser Pro Asp Ser Ser Ser Val Cys Val Gln Gly Arg
645 650 655
Cys Ile His Ala Gly Cys Asp Arg Ile Ile Gly Ser Lys Lys Lys Phe
660 665 670
Asp Lys Cys Met Val Cys Gly Gly Asp Gly Ser Gly Cys Ser Lys Gln
675 680 685
Ser Gly Ser Phe Arg Lys Phe Arg Tyr Gly Tyr Asn Asn Val Val Thr

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    690                 695                 700
Ile Pro Ala Gly Ala Thr His Ile Leu Val Arg Gln Gln Gly Asn Pro
705                 710                 715                 720
Gly His Arg Ser Ile Tyr Leu Ala Leu Lys Leu Pro Asp Gly Ser Tyr
                725                 730                 735
Ala Leu Asn Gly Glu Tyr Thr Leu Met Pro Ser Pro Thr Asp Val Val
            740                 745                 750
Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr Ala Ala Ser
        755                 760                 765
Glu Thr Leu Ser Gly His Gly Pro Leu Ala Gln Pro Leu Thr Leu Gln
    770                 775                 780
Val Leu Val Ala Gly Asn Pro Gln Asp Thr Arg Leu Arg Tyr Ser Phe
785                 790                 795                 800
Phe Val Pro Arg Pro Thr Pro Ser Thr Pro Arg Pro Thr Pro Gln Asp
                805                 810                 815
Trp Leu His Arg Arg Ala Gln Ile Leu Glu Ile Leu Arg Arg Arg Pro
            820                 825                 830
Trp Ala Gly Arg Lys Phe Ile Gly
        835                 840
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<210> 13
<211> 1518
<212> DNA
<213> Rattus norvegicus

<400> 13

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ctccagcgcc ggggtgctcc cgtagggcct tccggagacc ctacctctcg ctgcggggtg     300
gcctcgggct ggaaccccgc catcctgagg gccttggacc cttataaacc acggcggacg     360
ggcgtgggcg aaagccacaa ccggcgcagg tctgggcgcg ccaagcgctt cgtgtctata     420
ccacggtacg tggagacact ggtggtggcg gacgagtcaa tggtcaagtt tcacggcgcg     480
gatttggaac attatctgct gacgctgctg gccacggcgg cgcgactcta ccgccacccc     540
agcatcctca accctatcaa catcgttgtg gtcaaggtgt tactcttagg agatcgtgac     600
actgggccca aggtcacagg caacgcggcc ctgactctgc gcaacttctg tgcctggcag     660
aaaaagttga acaaagtgag cgacaagcac cccgagtact gggacacagc catcctcttc     720
accagacagg acctatgcgg ggctaccacc tgtgacacct tgggcatggc tgatgtgggc     780
accatgtgtg atcccaagag aagctgctct gtcatcgagg acgatgggct tccgtcggcc     840
ttcaccactg cccatgagct gggccatgtg ttcaacatgc cccatgacaa cgtgaaggtg     900
tgtgaggagg tgtttgggaa gctcagagcc aaccacatga tgtctccgac actcatccag     960
atcgaccgtg ccaacccctg gtcagcctgc agtgctgcca ttatcaccga cttcctggac    1020
agcgggcacg gtgactgcct cctggaccag cccagcaagc ccatcaccct gcctgaggac    1080
ctgccaggca caagctacag tttgagccaa cagtgcgagc tggcctttgg ggtgggctct    1140
aagccctgcc catatatgca gtactgtaca aagctgtggt gcaccggcaa ggccaagggg    1200
cagatggtgt gccagactcg ccacttcccc tgggcagatg gcaccagctg tggtgagggc    1260
aagttctgcc tcaagggagc ctgcgtggag agacacaacc caaacaagta ccgggtggac    1320
ggcccttggg ccaagtggga gccttatggt ccctgctcgc gcacctgcgg tgggggcgcg    1380
cagctggccc ggaggcaagt gcaagcaacc ctacccctgc caacgggcgg gaagtactgc    1440
gagggagtga gagtgaaata ccgatcttgc aacttggagc cctgccccag ctcagcctct    1500
ggcaagagct tccgggaa                                                   1518
```

<210> 14

<211> 505
<212> PRT
<213> Rattus norvegicus

<400> 14

Thr His Tyr Arg Ala Arg Ala Ala Ala Arg Ala Gly Gln Arg Leu Thr
1 5 10 15
Gly Ser Ser Leu Asp Leu Arg Arg Cys Phe Tyr Ser Gly Tyr Val Asn
20 25 30
Ala Glu Pro Asp Ser Phe Ala Ala Val Ser Leu Cys Gly Gly Leu Arg
35 40 45
Gly Ala Phe Gly Tyr Gln Gly Ala Glu Tyr Val Ile Ser Pro Leu Pro
50 55 60
Asn Thr Ser Ala Pro Glu Ala Gln Arg His Ser Gln Gly Ala His Leu
65 70 75 80
Leu Gln Arg Arg Gly Ala Pro Val Gly Pro Ser Gly Asp Pro Thr Ser
85 90 95
Arg Cys Gly Val Ala Ser Gly Trp Asn Pro Ala Ile Leu Arg Ala Leu
100 105 110
Asp Pro Tyr Lys Pro Arg Arg Thr Gly Val Gly Glu Ser His Asn Arg
115 120 125
Arg Arg Ser Gly Arg Ala Lys Arg Phe Val Ser Ile Pro Arg Tyr Val
130 135 140
Glu Thr Leu Val Val Ala Asp Glu Ser Met Val Lys Phe His Gly Ala
145 150 155 160
Asp Leu Glu His Tyr Leu Leu Thr Leu Leu Ala Thr Ala Ala Arg Leu
165 170 175
Tyr Arg His Pro Ser Ile Leu Asn Pro Ile Asn Ile Val Val Val Lys
180 185 190
Val Leu Leu Leu Gly Asp Arg Asp Thr Gly Pro Lys Val Thr Gly Asn
195 200 205
Ala Ala Leu Thr Leu Arg Asn Phe Cys Ala Trp Gln Lys Lys Leu Asn
210 215 220
Lys Val Ser Asp Lys His Pro Glu Tyr Trp Asp Thr Ala Ile Leu Phe
225 230 235 240
Thr Arg Gln Asp Leu Cys Gly Ala Thr Thr Cys Asp Thr Leu Gly Met
245 250 255
Ala Asp Val Gly Thr Met Cys Asp Pro Lys Arg Ser Cys Ser Val Ile
260 265 270
Glu Asp Asp Gly Leu Pro Ser Ala Phe Thr Thr Ala His Glu Leu Gly
275 280 285
His Val Phe Asn Met Pro His Asp Asn Val Lys Val Cys Glu Glu Val
290 295 300
Phe Gly Lys Leu Arg Ala Asn His Met Met Ser Pro Thr Leu Ile Gln
305 310 315 320
Ile Asp Arg Ala Asn Pro Trp Ser Ala Cys Ser Ala Ala Ile Ile Thr
325 330 335
Asp Phe Leu Asp Ser Gly His Gly Asp Cys Leu Leu Asp Gln Pro Ser
340 345 350
Lys Pro Ile Thr Leu Pro Glu Asp Leu Pro Gly Thr Ser Tyr Ser Leu
355 360 365
Ser Gln Gln Cys Glu Leu Ala Phe Gly Val Gly Ser Lys Pro Cys Pro
370 375 380
Tyr Met Gln Tyr Cys Thr Lys Leu Trp Cys Thr Gly Lys Ala Lys Gly
385 390 395 400

```
Gln Met Val Cys Gln Thr Arg His Phe Pro Trp Ala Asp Gly Thr Ser
                405                 410                 415
Cys Gly Glu Gly Lys Phe Cys Leu Lys Gly Ala Cys Val Glu Arg His
            420                 425                 430
Asn Pro Asn Lys Tyr Arg Val Asp Gly Pro Trp Ala Lys Trp Glu Pro
        435                 440                 445
Tyr Gly Pro Cys Ser Arg Thr Cys Gly Gly Gly Ala Gln Leu Ala Arg
    450                 455                 460
Arg Gln Val Gln Ala Thr Leu Pro Leu Pro Thr Gly Gly Lys Tyr Cys
465                 470                 475                 480
Glu Gly Val Arg Val Lys Tyr Arg Ser Cys Asn Leu Glu Pro Cys Pro
                485                 490                 495
Ser Ser Ala Ser Gly Lys Ser Phe Arg
            500                 505
```

```
<210> 15
<211> 1455
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1455)
<223> n = A,T,C or G

<400> 15
gatgcatcta agccctggtc caaatgcact tcagccacca tcacagaatt cctggatgat      60
ggccatggta actgtttgct ggacctacca cgaaagcaga tcctgggccc cgaagaactc     120
ccaggacaga cctacgatgc cacccagcag tgcaacctta cattcgggcc tgagtactcc     180
gtgtgtcccg gcatggatgt ctgtgctccc ctgtggtgtg ctgtggtacg ccagggccag     240
atggtctgtc tgaccaagaa gcttcctgcg gtggaaggga cgccttgtgg aaaggggaga     300
atctgcctgc agggcaaatg tgtggacaaa accaagaaaa aatattattc aacgtcaagc     360
catggcaact ggggatcttg gggatcctgg ggccagtgtt ctcgctcatg tggaggagga     420
gtgcagtttg cctatcgtcg ctgtaataac cctgctccca gaaacaacgg acgctactgc     480
acagggaaga gggccatcta ccgctcctgc agtctcatgc cctgcccacc caatggtaaa     540
tcatttcgtc atgaacagtg tgaggccaaa aatggctatc agtctgatgc aaaaggagtc     600
aaaacttttg tggaatgggt tcccaaatat gcaagtgtcc tgcccagcga tgtgtgcaag     660
ctgacctgca gagccaaagg gactggctac tatgtggtat tttctccaaa ggtgaccgat     720
ggcactgaat gtaggccgta cagtaattcc gtctgcgtcc gggggaagtg tgtgagaact     780
ggctgtgacg gcatcattgg ctcaaagctg cagtatgaca agtgcggagt atgtggagga     840
gacaactcca gctgtacaaa gattgttgga acctttaata agaaaagtaa gggttcanct     900
gacgtggtga ggattcctga aggggcaacc cacataaaag ttcgacagtt caaagccaaa     960
gaccagacta gattcactgc ctatttagcc ctgaaaaaga aaaacggtga gtaccttatc    1020
aatggaaagt acatgatctc cacttcagag actatcattg acatcaatgg aacagtcatg    1080
aactatagcg gttggagcca cagggatgac ttcctgcatg gcatgggcta ctctgccacg    1140
aaggaaattc taatagtgca gattcttgca acagacccca ctaaaccatt agatgtccgt    1200
tatagctttt ttgttcccaa gaagtccact ccaaaagtaa actctgtcac tagtcatggc    1260
agcaataaag tgggatcaca cacttcgcag ccgcagtggg tcacgggccc atggctcgcc    1320
tgctctagga cctgtgacac aggttggcac accagaacgg tgcagtgcca ggatggaaac    1380
cggaagttag caaaaggatg tcctctctcc caaaggcctt ctgcgtttaa gcaatgcttg    1440
ttgaagaaat gttag                                                      1455

<210> 16
<211> 484
```

<212> PRT
<213> Homo sapien

<220>
<221> VARIANT
<222> (1)...(484)
<223> Xaa = Any Amino Acid

<400> 16

```
Asp Ala Ser Lys Pro Trp Ser Lys Cys Thr Ser Ala Thr Ile Thr Glu
 1               5                  10                  15
Phe Leu Asp Asp Gly His Gly Asn Cys Leu Leu Asp Leu Pro Arg Lys
            20                  25                  30
Gln Ile Leu Gly Pro Glu Glu Leu Pro Gly Gln Thr Tyr Asp Ala Thr
        35                  40                  45
Gln Gln Cys Asn Leu Thr Phe Gly Pro Glu Tyr Ser Val Cys Pro Gly
    50                  55                  60
Met Asp Val Cys Ala Pro Leu Trp Cys Ala Val Val Arg Gln Gly Gln
65                  70                  75                  80
Met Val Cys Leu Thr Lys Lys Leu Pro Ala Val Glu Gly Thr Pro Cys
                85                  90                  95
Gly Lys Gly Arg Ile Cys Leu Gln Gly Lys Cys Val Asp Lys Thr Lys
            100                 105                 110
Lys Lys Tyr Tyr Ser Thr Ser Ser His Gly Asn Trp Gly Ser Trp Gly
        115                 120                 125
Ser Trp Gly Gln Cys Ser Arg Ser Cys Gly Gly Gly Val Gln Phe Ala
    130                 135                 140
Tyr Arg Arg Cys Asn Asn Pro Ala Pro Arg Asn Asn Gly Arg Tyr Cys
145                 150                 155                 160
Thr Gly Lys Arg Ala Ile Tyr Arg Ser Cys Ser Leu Met Pro Cys Pro
                165                 170                 175
Pro Asn Gly Lys Ser Phe Arg His Glu Gln Cys Glu Ala Lys Asn Gly
            180                 185                 190
Tyr Gln Ser Asp Ala Lys Gly Val Lys Thr Phe Val Glu Trp Val Pro
        195                 200                 205
Lys Tyr Ala Ser Val Leu Pro Ser Asp Val Cys Lys Leu Thr Cys Arg
    210                 215                 220
Ala Lys Gly Thr Gly Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp
225                 230                 235                 240
Gly Thr Glu Cys Arg Pro Tyr Ser Asn Ser Val Cys Val Arg Gly Lys
                245                 250                 255
Cys Val Arg Thr Gly Cys Asp Gly Ile Ile Gly Ser Lys Leu Gln Tyr
            260                 265                 270
Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Ile
        275                 280                 285
Val Gly Thr Phe Asn Lys Lys Ser Lys Gly Ser Xaa Asp Val Val Arg
    290                 295                 300
Ile Pro Glu Gly Ala Thr His Ile Lys Val Arg Gln Phe Lys Ala Lys
305                 310                 315                 320
Asp Gln Thr Arg Phe Thr Ala Tyr Leu Ala Leu Lys Lys Lys Asn Gly
                325                 330                 335
Glu Tyr Leu Ile Asn Gly Lys Tyr Met Ile Ser Thr Ser Glu Thr Ile
            340                 345                 350
Ile Asp Ile Asn Gly Thr Val Met Asn Tyr Ser Gly Trp Ser His Arg
        355                 360                 365
```

```
Asp Asp Phe Leu His Gly Met Gly Tyr Ser Ala Thr Lys Glu Ile Leu
    370                 375                 380
Ile Val Gln Ile Leu Ala Thr Asp Pro Thr Lys Pro Leu Asp Val Arg
385                 390                 395                 400
Tyr Ser Phe Phe Val Pro Lys Lys Ser Thr Pro Lys Val Asn Ser Val
                405                 410                 415
Thr Ser His Gly Ser Asn Lys Val Gly Ser His Thr Ser Gln Pro Gln
            420                 425                 430
Trp Val Thr Gly Pro Trp Leu Ala Cys Ser Arg Thr Cys Asp Thr Gly
        435                 440                 445
Trp His Thr Arg Thr Val Gln Cys Gln Asp Gly Asn Arg Lys Leu Ala
    450                 455                 460
Lys Gly Cys Pro Leu Ser Gln Arg Pro Ser Ala Phe Lys Gln Cys Leu
465                 470                 475                 480
Leu Lys Lys Cys


<210> 17
<211> 423
<212> DNA
<213> Bos taurus

<400> 17
tttagggagg agcagtgtga ggccaaaaat ggatatcagt ctgatgcaaa aggagtcaaa        60
acgtttgtgg aatgggttcc caaatatgct ggtgtcctgc ccggagacgt gtgcaaactg       120
acctgcagag ctaagggcac tggctactac gtggtgttct ctccaaaggt gaccgatggg       180
acagagtgca ggccatacag caattccgtg tgtgtccggg ggaagtgtgt gcggacaggc       240
tgtgacagca tcattggctc gaagctgcag tatgacaaat gtggcgtctg tggaggagac       300
aactccagtt gcacaaaggt ggtcggaacc ttcaataaaa aaagtaaggg ttacactgac       360
gtcgtgagga tccccgaagg ggcgactcac ataaaagtcc gacagttcaa agccaaagac       420
cag                                                                     423

<210> 18
<211> 141
<212> PRT
<213> Bos taurus

<400> 18
Phe Arg Glu Glu Gln Cys Glu Ala Lys Asn Gly Tyr Gln Ser Asp Ala
1               5                   10                  15
Lys Gly Val Lys Thr Phe Val Glu Trp Val Pro Lys Tyr Ala Gly Val
            20                  25                  30
Leu Pro Gly Asp Val Cys Lys Leu Thr Cys Arg Ala Lys Gly Thr Gly
        35                  40                  45
Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp Gly Thr Glu Cys Arg
    50                  55                  60
Pro Tyr Ser Asn Ser Val Cys Val Arg Gly Lys Cys Val Arg Thr Gly
65                  70                  75                  80
Cys Asp Ser Ile Ile Gly Ser Lys Leu Gln Tyr Asp Lys Cys Gly Val
                85                  90                  95
Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Val Val Gly Thr Phe Asn
            100                 105                 110
Lys Lys Ser Lys Gly Tyr Thr Asp Val Val Arg Ile Pro Glu Gly Ala
        115                 120                 125
Thr His Ile Lys Val Arg Gln Phe Lys Ala Lys Asp Gln
```

130 135 140

<210> 19
<211> 637
<212> DNA
<213> Bos taurus

<400> 19
ggaaaccctg gccatttgga gcaactacct ggccctgaag ctccccgatg gctcctatgc 60
cctcaacggt gaatacacgc tgatcccgtc ccccacagac gtggtactgc ccggggccgt 120
cagcctgcgc tacagcgggg ccactgcagc ctcggagaca ctgtcaggac acgggcccct 180
ggctgagccc ttaacgctgc aggtcctagt ggctggcaac ccgcagaacg cccgcctcag 240
atacagcttt ttcgtgccgc gaccgcgacc ggtcccctcc acgccacgcc ccactcccca 300
ggactggctg cgccgcaagt cacagattct ggagatcctc cggcggcgct cctgggccgg 360
caggaaataa cctcaccatc ccggctgccc tttctgggca ccggggcctc ggacttagct 420
gggtgaacga gagacctctg cagcggcctc accccgagac atcgtggggg aggggcttag 480
tgagccccgc ctctcctccc cgcgctaccg agcaggctgg ccctgccggg gtttcctgcc 540
ctggatggct ggtggatgga aggggctggg agattgtccc ctatctaaac tgccccctct 600
gccctgctgg tcacaggagg gagggggaag gcaggga 637

<210> 20
<211> 122
<212> PRT
<213> Bos taurus

<400> 20
Glu Thr Leu Ala Ile Trp Ser Asn Tyr Leu Ala Leu Lys Leu Pro Asp
1 5 10 15
Gly Ser Tyr Ala Leu Asn Gly Glu Tyr Thr Leu Ile Pro Ser Pro Thr
20 25 30
Asp Val Val Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr
35 40 45
Ala Ala Ser Glu Thr Leu Ser Gly His Gly Pro Leu Ala Glu Pro Leu
50 55 60
Thr Leu Gln Val Leu Val Ala Gly Asn Pro Gln Asn Ala Arg Leu Arg
65 70 75 80
Tyr Ser Phe Phe Val Pro Arg Pro Arg Pro Val Pro Ser Thr Pro Arg
85 90 95
Pro Thr Pro Gln Asp Trp Leu Arg Arg Lys Ser Gln Ile Leu Glu Ile
100 105 110
Leu Arg Arg Arg Ser Trp Ala Gly Arg Lys
115 120

<210> 21
<211> 1143
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1143)
<223> n = A,T,C or G

<400> 21
actcactata gggctcgtgc ggccgcccgg gcaggtatct ttaagcatcc cagcatcctc 60

```
aaccccatca acatcgttgt ggtcaaggtg ctgcttctta gagatcgtga ctccgggccc    120
aaggtcaccg gcaatgcggc cctgacgctg cgcaacttct gtgcctggca gaagaagctg    180
aacaaagtga gtgacaagca ccccgagtac tgggacactg ccatcctctt caccaggcag    240
gacctgtgtg gagccaccac ctgtgacacc ctgggcatgg ctgatgtggg taccatgtgt    300
gaccccaaga gaagctgctc tgtcattgag gacgatgggc ttccatcagc cttcaccact    360
gcccacgagc tgggccacgt gttcaacatg ccccatgaca atgtgaaagt ctgtgaggag    420
gtgtttggga agctccgagc caaccacatg atgtccccga ccctcatcca gatcgaccgt    480
gccaacccct ggtcagcctg cagtgctgcc atcatcaccg actttctgga cagcgggcac    540
ggtgactgcc tcctggacca acccagcaag cccatcttcc tgccgagnga tctgccgggc    600
gccagctaca ccctgagcca gcartgcgag ctggcttttg gcgtgggctt caagccctgt    660
ccttacatgc agtactgcac caagctgtgg tgcaccggga aggccaaggg acagatggtg    720
tgccaaaccc gccacttccc ctgggccgat ggcaccagtt gtggcgaggg caagttctgc    780
ctcaaagggg cctgcgtgga aaracacaac ctcaacaagc acagggtgga tggttcctgg    840
gccaaatggg atccctatgg cccctgctcg cgcacatgtg gtgggggcgt gcagctggcc    900
aggaggcagn tgcaccaacc ccancccctg ccaacngggg gcaagtactg cgagggagtg    960
agggtgaaat accgatcctg caacctggag ccctgcccca gctcagcctc cggaaagagc   1020
ttccgggagg agcagtgtga ggctttcaac ggctacaacc acagcaccaa ccggctcact   1080
ctcgccgtgg catgggtgcc caagtactcc ggcgtgtctc cccgtgacaa gtgtaagctc   1140
atc                                                                  1143
```

<210> 22
<211> 381
<212> PRT
<213> Homo sapien

<220>
<221> VARIANT
<222> (1)...(381)
<223> Xaa = Any Amino Acid

<400> 22

```
Thr His Tyr Arg Ala Arg Ala Ala Ala Arg Ala Gly Ile Phe Lys His
 1               5                  10                  15
Pro Ser Ile Leu Asn Pro Ile Asn Ile Val Val Val Lys Val Leu Leu
            20                  25                  30
Leu Arg Asp Arg Asp Ser Gly Pro Lys Val Thr Gly Asn Ala Ala Leu
        35                  40                  45
Thr Leu Arg Asn Phe Cys Ala Trp Gln Lys Lys Leu Asn Lys Val Ser
    50                  55                  60
Asp Lys His Pro Glu Tyr Trp Asp Thr Ala Ile Leu Phe Thr Arg Gln
65                  70                  75                  80
Asp Leu Cys Gly Ala Thr Thr Cys Asp Thr Leu Gly Met Ala Asp Val
                85                  90                  95
Gly Thr Met Cys Asp Pro Lys Arg Ser Cys Ser Val Ile Glu Asp Asp
            100                 105                 110
Gly Leu Pro Ser Ala Phe Thr Thr Ala His Glu Leu Gly His Val Phe
        115                 120                 125
Asn Met Pro His Asp Asn Val Lys Val Cys Glu Glu Val Phe Gly Lys
    130                 135                 140
Leu Arg Ala Asn His Met Met Ser Pro Thr Leu Ile Gln Ile Asp Arg
145                 150                 155                 160
Ala Asn Pro Trp Ser Ala Cys Ser Ala Ala Ile Ile Thr Asp Phe Leu
                165                 170                 175
Asp Ser Gly His Gly Asp Cys Leu Leu Asp Gln Pro Ser Lys Pro Ile
            180                 185                 190
```

```
Phe Leu Pro Xaa Asp Leu Pro Gly Ala Ser Tyr Thr Leu Ser Gln Gln
        195                 200                 205
Cys Glu Leu Ala Phe Gly Val Gly Phe Lys Pro Cys Pro Tyr Met Gln
    210                 215                 220
Tyr Cys Thr Lys Leu Trp Cys Thr Gly Lys Ala Lys Gly Gln Met Val
225                 230                 235                 240
Cys Gln Thr Arg His Phe Pro Trp Ala Asp Gly Thr Ser Cys Gly Glu
                245                 250                 255
Gly Lys Phe Cys Leu Lys Gly Ala Cys Val Glu Xaa His Asn Leu Asn
            260                 265                 270
Lys His Arg Val Asp Gly Ser Trp Ala Lys Trp Asp Pro Tyr Gly Pro
        275                 280                 285
Cys Ser Arg Thr Cys Gly Gly Gly Val Gln Leu Ala Arg Arg Gln Xaa
    290                 295                 300
His Gln Pro Xaa Pro Leu Pro Thr Gly Gly Lys Tyr Cys Glu Gly Val
305                 310                 315                 320
Arg Val Lys Tyr Arg Ser Cys Asn Leu Glu Pro Cys Pro Ser Ser Ala
                325                 330                 335
Ser Gly Lys Ser Phe Arg Glu Glu Gln Cys Glu Ala Phe Asn Gly Tyr
            340                 345                 350
Asn His Ser Thr Asn Arg Leu Thr Leu Ala Val Ala Trp Val Pro Lys
        355                 360                 365
Tyr Ser Gly Val Ser Pro Arg Asp Lys Cys Lys Leu Ile
    370                 375                 380
```

<210> 23
<211> 297
<212> DNA
<213> Rattus norvegicus

<400> 23

```
tccgcccttc cgggaggaac agtgtgaaaa atataatgcc tacaaccaca cggacctgga      60
tgggaatttc cttcagtggg tccccaaata ctcaggagtg tccccccgag accgatgcaa     120
actgttttgc agagcccgtg ggaggagtga gttcaaagtg tttgaaacta aggtgatcga     180
tggcactctg tgcggaccgg atactctggc catctgtgtg cggggacagt gcgttaaggc     240
tggctgtgac catgtggtga actcacctaa gaagctggac aagtgcggta tctgtgg        297
```

<210> 24
<211> 98
<212> PRT
<213> Rattus norvegicus

<400> 24

```
Pro Pro Phe Arg Glu Glu Gln Cys Glu Lys Tyr Asn Ala Tyr Asn His
 1               5                  10                  15
Thr Asp Leu Asp Gly Asn Phe Leu Gln Trp Val Pro Lys Tyr Ser Gly
            20                  25                  30
Val Ser Pro Arg Asp Arg Cys Lys Leu Phe Cys Arg Ala Arg Gly Arg
        35                  40                  45
Ser Glu Phe Lys Val Phe Glu Thr Lys Val Ile Asp Gly Thr Leu Cys
    50                  55                  60
Gly Pro Asp Thr Leu Ala Ile Cys Val Arg Gly Gln Cys Val Lys Ala
65                  70                  75                  80
Gly Cys Asp His Val Val Asn Ser Pro Lys Lys Leu Asp Lys Cys Gly
                85                  90                  95
```

Ile Cys

<210> 25
<211> 823
<212> DNA
<213> Rattus norvegicus

<400> 25
cccctggatg tggtcaaagt gcagtcggaa gtacatcacc gagttcttag acactgggta 60
tggagagtgc ttgttaaatg aacctcaatc caggacctat cctttgcctt cccaactgcc 120
cggccttctc tacaacgtga ataaacaatg tgaactgatt tttggaccag gctctcaagt 180
gtgcccatat atgatgcagt gcagacggct ctggtgcaat aacgtggatg gagcacacaa 240
aggctgcagg actcagcaca cgccctgggc agatggaacc gagtgtgagc ctggaaagca 300
ctgcaagttt ggattctgtg ttcccaaaga aatggagggc cctgcaattg atggatcctg 360
gggaagttgg agtcactttg gggcctgctc aagaacatgt ggaggaggca tcagaacagc 420
catcagagag tgcaacagac cagagccaaa aaatggtggg aggtactgtg tagggaggag 480
aatraagttc aaatcctgca acaccgagcc ctgcccgaag cacaagcgag acttccgtga 540
ggagcagtgt gcttactttg acggcaagca tttcaacatc aatggtctgc tgcccagtgt 600
acgctgggtc cctaagtaca gtggaatttt gatgaaggac cgatgcaagt tgttctgcag 660
agtggcagga aacacagcct actaccagct tcgagacaga gtgattgacg gaacccccctg 720
tggccaggac acaaatgaca tctgtgtcca aggcctttgc cggcaagctg gatgtgatca 780
tactttaaac tcaaaggccc ggaaagataa atgtgggatt tgt 823

<210> 26
<211> 274
<212> PRT
<213> Rattus norvegicus

<220>
<221> VARIANT
<222> (1)...(274)
<223> Xaa = Any Amino Acid

<400> 26
Pro Trp Met Trp Ser Lys Cys Ser Arg Lys Tyr Ile Thr Glu Phe Leu
1 5 10 15
Asp Thr Gly Tyr Gly Glu Cys Leu Leu Asn Glu Pro Gln Ser Arg Thr
20 25 30
Tyr Pro Leu Pro Ser Gln Leu Pro Gly Leu Leu Tyr Asn Val Asn Lys
35 40 45
Gln Cys Glu Leu Ile Phe Gly Pro Gly Ser Gln Val Cys Pro Tyr Met
50 55 60
Met Gln Cys Arg Arg Leu Trp Cys Asn Asn Val Asp Gly Ala His Lys
65 70 75 80
Gly Cys Arg Thr Gln His Thr Pro Trp Ala Asp Gly Thr Glu Cys Glu
85 90 95
Pro Gly Lys His Cys Lys Phe Gly Phe Cys Val Pro Lys Glu Met Glu
100 105 110
Gly Pro Ala Ile Asp Gly Ser Trp Gly Ser Trp Ser His Phe Gly Ala
115 120 125
Cys Ser Arg Thr Cys Gly Gly Gly Ile Arg Thr Ala Ile Arg Glu Cys
130 135 140
Asn Arg Pro Glu Pro Lys Asn Gly Gly Arg Tyr Cys Val Gly Arg Arg
145 150 155 160

Xaa Lys Phe Lys Ser Cys Asn Thr Glu Pro Cys Pro Lys His Lys Arg
165 170 175
Asp Phe Arg Glu Glu Gln Cys Ala Tyr Phe Asp Gly Lys His Phe Asn
180 185 190
Ile Asn Gly Leu Leu Pro Ser Val Arg Trp Val Pro Lys Tyr Ser Gly
195 200 205
Ile Leu Met Lys Asp Arg Cys Lys Leu Phe Cys Arg Val Ala Gly Asn
210 215 220
Thr Ala Tyr Tyr Gln Leu Arg Asp Arg Val Ile Asp Gly Thr Pro Cys
225 230 235 240
Gly Gln Asp Thr Asn Asp Ile Cys Val Gln Gly Leu Cys Arg Gln Ala
245 250 255
Gly Cys Asp His Thr Leu Asn Ser Lys Ala Arg Lys Asp Lys Cys Gly
260 265 270
Ile Cys

<210> 27
<211> 1073
<212> PRT
<213> Homo sapien

<400> 27
Met Gln Phe Val Ser Trp Ala Thr Leu Leu Thr Leu Leu Val Arg Asp
1 5 10 15
Leu Ala Glu Met Gly Ser Pro Asp Ala Ala Ala Ala Val Arg Lys Asp
20 25 30
Arg Leu His Pro Arg Gln Val Lys Leu Leu Glu Thr Leu Gly Glu Tyr
35 40 45
Glu Ile Val Ser Pro Ile Arg Val Asn Ala Leu Gly Glu Pro Phe Pro
50 55 60
Thr Asn Val His Phe Lys Arg Thr Arg Arg Ser Ile Asn Ser Ala Thr
65 70 75 80
Asp Pro Trp Pro Ala Phe Ala Ser Ser Ser Ser Ser Ser Thr Ser Ser
85 90 95
Gln Ala His Tyr Arg Leu Ser Ala Phe Gly Gln Gln Phe Leu Phe Asn
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Leu Thr Ala Asn Ala Gly Phe Ile Ala Pro Leu Phe Thr Val Thr Leu
115 120 125
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130 135 140
Ala Glu Leu Lys His Cys Phe Tyr Lys Gly Tyr Val Asn Thr Asn Ser
145 150 155 160
Glu His Thr Ala Val Ile Ser Leu Cys Ser Gly Met Leu Gly Thr Phe
165 170 175
Arg Ser His Asp Gly Asp Tyr Phe Ile Glu Pro Leu Gln Ser Met Asp
180 185 190
Glu Gln Glu Asp Glu Glu Glu Gln Asn Lys Pro His Ile Ile Tyr Arg
195 200 205
Arg Ser Ala Pro Gln Arg Glu Pro Ser Thr Gly Arg His Ala Cys Asp
210 215 220
Thr Ser Glu His Lys Asn Arg His Ser Lys Asp Lys Lys Lys Thr Arg
225 230 235 240
Ala Arg Lys Trp Gly Glu Arg Ile Asn Leu Ala Gly Asp Val Ala Ala
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Leu Asn Ser Gly Leu Ala Thr Glu Ala Phe Ser Ala Tyr Gly Asn Lys

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Ile Leu Tyr Asn Val Asn Lys Gln Cys Glu Leu Ile Phe Gly Pro Gly
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625                 630                 635                 640
Pro Cys Leu Lys Gln Lys Arg Asp Phe Arg Asp Glu Gln Cys Ala His
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Phe Asp Gly Lys His Phe Asn Ile Asn Gly Leu Leu Pro Asn Val Arg
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Trp Val Pro Lys Tyr Ser Gly Ile Leu Met Lys Asp Arg Cys Lys Leu
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Phe Cys Arg Val Ala Gly Asn Thr Ala Tyr Tyr Gln Leu Arg Asp Arg
    690                 695                 700
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Val Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val
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Gln Gly Leu Cys Arg Gln Ala Gly Cys Asp His Val Leu Asn Ser Lys
725 730 735
Ala Arg Arg Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys
740 745 750
Lys Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr
755 760 765
Val Val Arg Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Arg Gln His
770 775 780
Ser Phe Ser Gly Glu Thr Asp Asp Asp Asn Tyr Leu Ala Leu Ser Ser
785 790 795 800
Ser Lys Gly Glu Phe Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala
805 810 815
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Glu Thr Ala Val Glu Arg Ile Asn Ser Thr Asp Arg Ile Glu Gln Glu
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850 855 860
Arg Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr
865 870 875 880
Trp Asn Ser His Gly Pro Trp Gln Ala Cys Ser Lys Pro Cys Gln Gly
885 890 895
Glu Arg Lys Arg Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr
900 905 910
Val Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr
915 920 925
Glu Pro Cys Gly Thr Asp Cys Asp Leu Arg Trp His Val Ala Ser Arg
930 935 940
Ser Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile
945 950 955 960
Tyr Cys Ala Lys Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp
965 970 975
Asp Gly Phe Cys Ser Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys
980 985 990
Ser Gly Glu Cys Asn Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu
995 1000 1005
Cys Lys Ser Lys Ser Cys Asp Gly Gly Thr Gln Arg Arg Arg Ala Ile
1010 1015 1020
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1025 1030 1035 1040
Gln Glu Lys Val Thr Ile Gln Arg Cys Ser Glu Phe Pro Cys Pro Gln
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<212> PRT
<213> Mus musculus

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65                  70                  75                  80
Ser Gly Phe Leu Ala Pro Gly Phe Thr Leu Gln Thr Val Gly Arg Ser
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Pro Gly Ser Glu Ala Gln His Leu Asp Pro Thr Gly Asp Leu Ala His
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Cys Phe Tyr Ser Gly Thr Val Asn Gly Asp Pro Gly Ser Ala Ala Ala
        115                 120                 125
Leu Ser Leu Cys Glu Gly Val Arg Gly Ala Phe Tyr Leu Gln Gly Glu
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Glu Phe Phe Ile Gln Pro Ala Pro Gly Val Ala Thr Glu Arg Leu Ala
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Pro Ala Val Pro Glu Glu Glu Ser Ser Ala Arg Pro Gln Phe His Ile
                165                 170                 175
Leu Arg Arg Arg Arg Arg Gly Ser Gly Gly Ala Lys Cys Gly Val Met
            180                 185                 190
Asp Asp Glu Thr Leu Pro Thr Ser Asp Ser Arg Pro Glu Ser Gln Asn
        195                 200                 205
Thr Arg Asn Gln Trp Pro Val Arg Asp Pro Thr Pro Gln Asp Ala Gly
    210                 215                 220
Lys Pro Ser Gly Pro Gly Ser Ile Arg Lys Lys Arg Phe Val Ser Ser
225                 230                 235                 240
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Ala Ala Arg Phe Tyr Lys His Pro Ser Ile Arg Asn Ser Ile Ser Leu
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Val Val Val Lys Ile Leu Val Ile Tyr Glu Glu Gln Lys Gly Pro Glu
    290                 295                 300
Val Thr Ser Asn Ala Ala Leu Thr Leu Arg Asn Phe Cys Asn Trp Gln
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Lys Gln His Asn Ser Pro Ser Asp Arg Asp Pro Glu His Tyr Asp Thr
                325                 330                 335
Ala Ile Leu Phe Thr Arg Gln Asp Leu Cys Gly Ser His Thr Cys Asp
            340                 345                 350
Thr Leu Gly Met Ala Asp Val Gly Thr Val Cys Asp Pro Ser Arg Ser
        355                 360                 365
Cys Ser Val Ile Glu Asp Asp Gly Leu Gln Ala Ala Phe Thr Thr Ala
    370                 375                 380
His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Ala Lys His
385                 390                 395                 400
Cys Ala Ser Leu Asn Gly Val Thr Gly Asp Ser His Leu Met Ala Ser
                405                 410                 415
Met Leu Ser Ser Leu Asp His Ser Gln Pro Trp Ser Pro Cys Ser Ala
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Tyr Met Val Thr Ser Phe Leu Asp Asn Gly His Gly Glu Cys Leu Met
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Lys His Cys Pro Asp Ala Ala Ser Thr Cys Thr Thr Leu Trp Cys Thr
                485                 490                 495
Gly Thr Ser Gly Gly Leu Leu Val Cys Gln Thr Lys His Phe Pro Trp
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Ala Asp Gly Thr Ser Cys Gly Glu Gly Lys Trp Cys Val Ser Gly Lys
        515                 520                 525
Cys Val Asn Lys Thr Asp Met Lys His Phe Ala Thr Pro Val His Gly
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Asn Gly Gly Lys Tyr Cys Glu Gly Lys Arg Val Arg Tyr Arg Ser Cys
            580                 585                 590
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705                 710                 715                 720
Gly Tyr His Asp Ile Val Thr Ile Pro Ala Gly Ala Thr Asn Ile Glu
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Val Lys His Arg Asn Gln Arg Gly Ser Arg Asn Asn Gly Ser Phe Leu
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Ala Ile Arg Ala Ala Asp Gly Thr Tyr Ile Leu Asn Gly Asn Phe Thr
        755                 760                 765
Leu Ser Thr Leu Glu Gln Asp Leu Thr Tyr Lys Gly Thr Val Leu Arg
    770                 775                 780
Tyr Ser Gly Ser Ser Ala Ala Leu Glu Arg Ile Arg Ser Phe Ser Pro
785                 790                 795                 800
Leu Lys Glu Pro Leu Thr Ile Gln Val Leu Met Val Gly His Ala Leu
                805                 810                 815
Arg Pro Lys Ile Lys Phe Thr Tyr Phe Met Lys Lys Lys Thr Glu Ser
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Phe Asn Ala Ile Pro Thr Phe Ser Glu Trp Val Ile Glu Glu Trp Gly
        835                 840                 845
Glu Cys Ser Lys Thr Cys Gly Ser Gly Trp Gln Arg Arg Val Val Gln
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1 5

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<213> Artificial Sequence

<220>
<223> Oligonucleotide derived from analysis of the
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<222> (1)...(18)
<223> n = A,T,C or G

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ttymgngarg arcartgy 18

<210> 34
<211> 18
<212> DNA
<213> Artificial Sequence

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sequences from ADAMTS-1 (mouse) and ADAMTS-3 (rat)

<221> misc_feature
<222> (1)...(18)
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<212> PRT
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<223> Consensus catalytic sequence site based on ADAM
and snake venom metalloproteases

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<221> VARIANT
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<223> Xaa = Any Amino Acid

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<210> 36
<211> 7
<212> PRT
<213> Unknown

<220>
<223> Conserved heparin binding segment of internal TSP1
motif of ADAM-TS family members

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<223> Xaa = Serine of Glycine

<221> VARIANT
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<210> 37
<211> 6
<212> PRT
<213> Unknown

<220>
<223> Conserved heparin binding segment of internal TSP1
motif of ADAM-TS family members

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<400> 38

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<210> 40
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<210> 41
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<220>
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<211> 12
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<213> Unknown

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<210> 43
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<210> 44
<211> 12
<212> PRT
<213> Unknown

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1 5 10

<210> 45
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<212> PRT
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1 5 10

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1 5 10

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1 5 10

<210> 49
<211> 12
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<213> Homo sapien

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<400> 50
His Glu Leu Gly His Val Phe Ser Ile Pro His Asp
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<210> 51
<211> 12
<212> PRT
<213> Unknown

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<221> VARIANT
<222> (1)...(12)
<223> Xaa = Any Amino Acid

<400> 51
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US00/06237

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(25) Filing Language: English

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(71) Applicant *(for all designated States except US)*: **NEUROCRINE BIOSCIENCES, INC.** [US/US]; 10555 Science Center Drive, San Diego, CA 92121 (US).

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(74) Agents: **CHRISTIANSEN, William, T.** et al.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

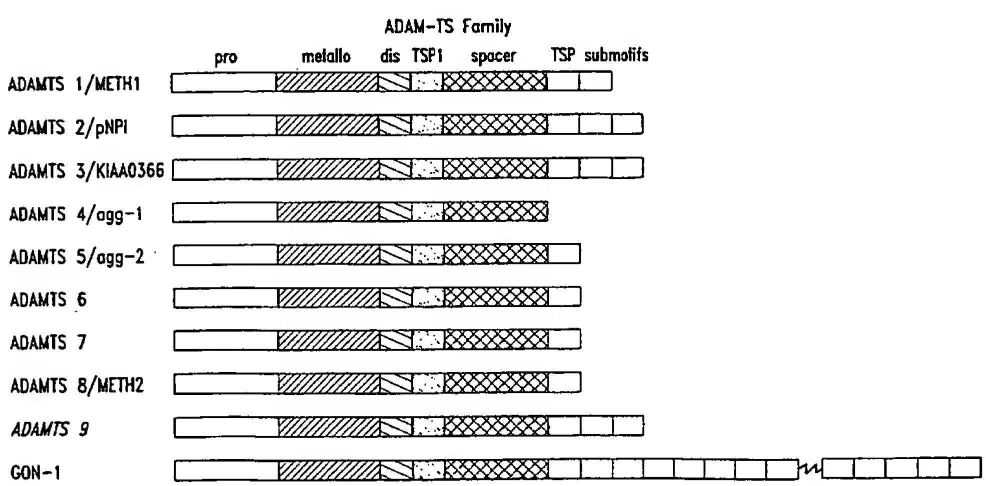
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report: 18 January 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METALLOPROTEINASES AND METHODS OF USE THEREFOR



(57) Abstract: Members of the ADAMTS family of metalloproteinases are provided, along with variants thereof and agents that modulate an activity of such metalloproteinases. The polypeptides and modulating agents may be used, for example, in the prevention and treatment of a variety of conditions associated with undesirable levels of metalloproteinase activity.

WO 00/53774 A3

INTERNATIONAL SEARCH REPORT

International Application No
I ./US 00/06237

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/57 C12N15/63 C12N9/64 A61K38/48 C07K16/40
C12Q1/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N A61K C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 55643 A (KUREHA CHEMICAL INDUSTRY CO., LTD.) 10 December 1998 (1998-12-10) & EP 1 004 674 A (KUREHA CHEMICAL INDUSTRY CO.,LTD.) 31 May 2000 (2000-05-31) ---	1,3-11, 17-21, 28,29, 31,32

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2000	13.10.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	MONTERO LOPEZ B.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOUJI KUNO ET AL.: "Molecular cloning of a gene encoding a new type of metalloproteinase-disintegrin family protein with thrombospondin motifs as an inflammation associated gene" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 1, 3 January 1997 (1997-01-03), pages 556-562, XP002076038 MD US cited in the application abstract page 558, left-hand column, paragraph 2 -page 559, left-hand column, paragraph 2; figure 2 page 559, left-hand column, paragraph 4 page 561, right-hand column, last paragraph -page 562, left-hand column, paragraph 1 ---	1,3-11, 17,20, 21,28, 29,31,32
X	KOUJI KUNO ET AL.: "The exon/intron organization and chromosomal mapping of the mouse ADAMTS-1 gene encoding an ADAM family protein with TPS motifs" GENOMICS, vol. 46, no. 3, 15 December 1997 (1997-12-15), pages 466-471, XP000922766 cited in the application page 466, right-hand column, paragraph 2 page 468, left-hand column, paragraph 5 -page 470, right-hand column, paragraph 2; figure 3 ---	1,3-11
X	BOR LUEN TANG ET AL.: "ADAMTS: A novel family of proteases with an ADAM protease domain and thrombospondin 1 repeats" FEBS LETTERS, [Online] vol. 445, 26 February 1999 (1999-02-26), pages 223-225, XP002141413 AMSTERDAM NL Retrieved from the Internet: <URL:http://gdbwww.gdb.org/gdb-bin/genera/genera/hgd/Gene?!action=query&displayName=ADAMTS2> [retrieved on 2000-06-22] page 223, left-hand column, paragraph 2 -page 225, right-hand column, paragraph 2; figure 2 ---	1,3-11
X	EMBL Database Entry AI378857 Accession number AI378857; 28 January 1999 ROBERT STRAUSBERG:"tc67h11.x1 Soares_NhHMPu_S1 Homo sapiens cDNA clone" XP002141415 the whole document ---	1,5-7

-/--

1

International Application No
P ./US 00/06237

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	FRANCISCA VÂZQUEZ ET AL.: "METH-1, a human ortholog of ADAMTS-1, and METH-2 are members of a new family of proteins with angio-inhibitory activity" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 33, 13 August 1999 (1999-08-13), pages 23349-23357, XP002141414 MD US abstract page 23349, right-hand column, paragraph 2 -page 23350, left-hand column, paragraph 1 page 23351, left-hand column, paragraph 1 -page 23352, right-hand column, paragraph 2; figure 1 page 23353, left-hand column, paragraph 4 -page 23357, left-hand column, paragraph 2	1,3-6, 8-11

INTERNATIONAL SEARCH REPORT

Int...ational application No.
PCT/US 00/06237

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 22-27, 30, 33-35
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-12, 17-35 (partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 22-27, 30, 33-35

Present claims 22-27, 30 and 33-35 relate to an agent defined by reference to a desirable characteristic or property, namely decreasing or modulating expression or activity of an ADAMTS protein. The claims cover all agents having this characteristic or property, whereas the application does not provide support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any specific example of such agents. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the agent by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for claims 22-27, 30 and 33-35.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:1 or 23 encoding ADAMTS-2; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-2 polypeptide; ADAMTS-2 polypeptide of SEQ ID NO:2 or 24 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-2 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-2 protein

2. Claims: 36 and partially 1-12, 17-35

Polynucleotide of SEQ ID NO:3, 15 or 17 encoding ADAMTS-4; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-4 polypeptide; ADAMTS-4 polypeptide of SEQ ID NO:4, 16 or 18 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-4 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-4 protein

3. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:9 or 25 encoding ADAMTS-3; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-3 polypeptide; ADAMTS-3 polypeptide of SEQ ID NO:10 or 26 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-3 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-3 protein

4. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:13 or 21 encoding ADAMTS-5; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-5 polypeptide; ADAMTS-5 polypeptide of SEQ ID NO:13 or 21 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-5 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-5 protein

5. Claims: Partially, 1, 3-12, 17-35

Polynucleotide encoding an ADAMTS-9 protein of SEQ ID NO:27;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-9 polypeptide; ADAMTS-9 polypeptide of SEQ ID NO:27 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-9 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-9 protein

6. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:6 or a variant thereof; ADAMTS polypeptide of SEQ ID NO:6 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

7. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:8 or a variant thereof; ADAMTS polypeptide of SEQ ID NO:8 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

8. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:12 or 20 or variants thereof; ADAMTS polypeptide of SEQ ID NO:12 or 20 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

INTERNATIONAL SEARCH REPORT

'nformation on patent family members

International Application No

F ./US 00/06237

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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